```
=> d his

     (FILE 'HOME' ENTERED AT 14:23:33 ON 03 JAN 2007)

     FILE 'REGISTRY' ENTERED AT 14:23:42 ON 03 JAN 2007
L1                STRUCTURE UPLOADED
L2                STRUCTURE UPLOADED
L3                STRUCTURE UPLOADED
L4              8 S L1 OR L2
L5             56 S L4 FULL
L6             11 S L3
L7            377 S L3 FULL

     FILE 'CAPLUS' ENTERED AT 14:26:02 ON 03 JAN 2007
L8             11 S L5/P
L9           5837 S L7
L10            10 S L8 AND L9

=> d que l10 stat
L1                STR
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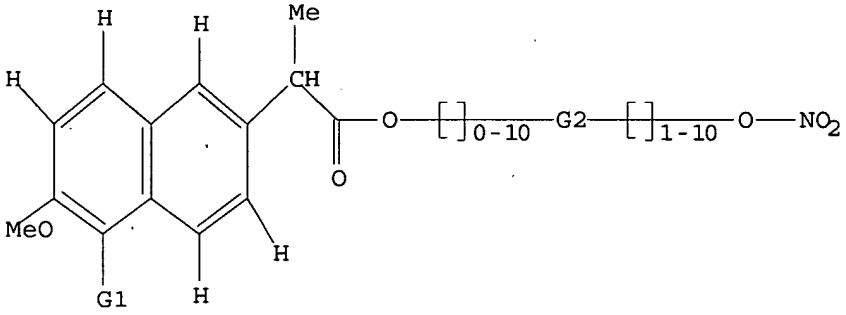
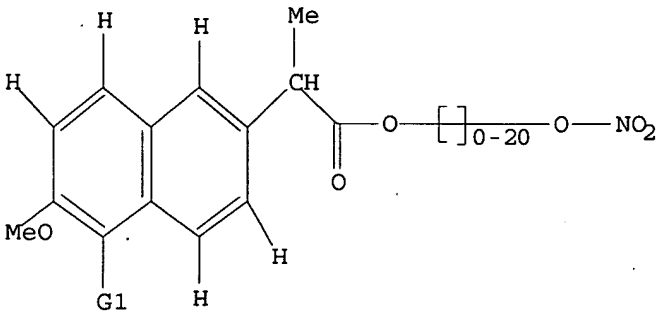


G1 H,Br

G2 O,S,N,P,Cy

Structure attributes must be viewed using STN Express query preparation.

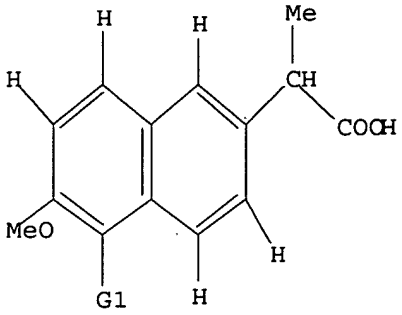
L2 STR



G1 H,Br

Structure attributes must be viewed using STN Express query preparation.

L3 STR



G1 H,Br

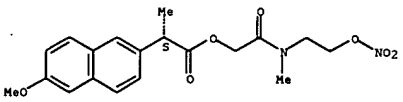
Structure attributes must be viewed using STN Express query preparation.

L5	56	SEA	FILE=REGISTRY	SSS FUL	L1 OR L2
L7	377	SEA	FILE=REGISTRY	SSS FUL	L3
L8	11	SEA	FILE=CAPLUS ABB=ON	PLU=ON	L5/P
L9	5837	SEA	FILE=CAPLUS ABB=ON	PLU=ON	L7
L10	10	SEA	FILE=CAPLUS ABB=ON	PLU=ON	L8 AND L9

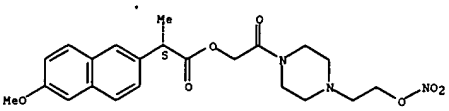
=> d 1-10 bib abs hitstr

L10 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:228540 CAPLUS
DN 144:460283
TI Synthesis and anti-inflammatory activity of a series of N-substituted naproxen glycolamides: Nitric oxide-donor naproxen prodrugs
AU Ranatunge, Ramani R.; Augustyniak, Michael E.; Dhawan, Vijay; Ellis, James L.; Garvey, David S.; Janero, David R.; Letts, L. Gordon; Richardson, Stewart K.; Shumway, Mathew J.; Trocha, A. Mark; Young, Delano V.; Zemtseva, Irina S.
CS NitroMed, Inc., Lexington, MA, 02421, USA
SO Bioorganic & Medicinal Chemistry (2006), 14(8), 2589-2599
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier B.V.
DT Journal
LA English
OS CASREACT 144:460283
AB A series of glycolamide naproxen prodrugs containing a nitrate group as a nitric oxide (NO) donor moiety has been synthesized. These compds. were evaluated for their anti-inflammatory activity, naproxen release, and gastric tolerance. Compds. 4a, 4b, 5a, 5b, 7b, and 7c exhibited anti-inflammatory activity equivalent to that of the parent NSAID, naproxen-Na, in the rat carrageenan paw edema model. At equimolar doses relative to naproxen-Na, the NO-donor glycolamide derivs. 4a, 4b, 5a, 5b, 7b, and 7c were gastro-sparing in the rat. Naproxen formation from these NO-donor glycolamides varied among the structures examined, with the N-substituent on the amide group having a particular influence, and demonstrated their prodrug nature. Compound 7b was selected for exemplary demonstration that the glycolamide nitrates can be bioactivated to release NO. These data open the possibility that naproxen glycolamide nitrates may represent a safer alternative to naproxen as anti-inflammatory medicines.
IT 646509-88-8P, [N-Methyl-N-[2-(nitrooxy)ethyl]carbamoyl]methyl(2S)-2-[6-methoxy(2-naphthyl)propanoate 646509-94-6P, [N-Ethyl-N-[2-(nitrooxy)ethyl]carbamoyl]methyl-[(2S)-2-[6-methoxy(2-naphthyl)propanoate 646509-98-0P 646510-52-3P 646510-72-7P 646510-77-2P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and antiinflammatory activity of substituted naproxen glycolamides)
RN 646509-88-8 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[methyl[2-(nitrooxy)ethyl]amino]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



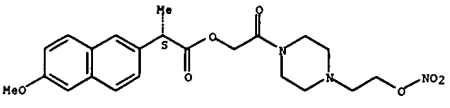
L10 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



● HCl

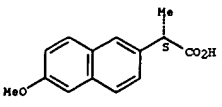
RN 646510-77-2 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[4-[2-(nitrooxy)ethyl]-1-piperazinyl]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 22204-53-1, Naproxen
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(synthesis and antiinflammatory activity of substituted naproxen glycolamides)
RN 22204-53-1 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

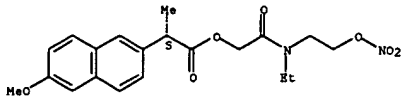
Absolute stereochemistry. Rotation (+).



IT 886458-14-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and antiinflammatory activity of substituted naproxen glycolamides)
RN 886458-14-6 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[cyclohexyl[2-(nitrooxy)ethyl]amino]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

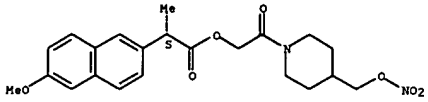
L10 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 646509-94-6 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[ethyl[2-(nitrooxy)ethyl]amino]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



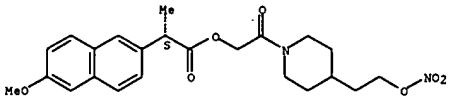
RN 646509-98-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[4-[(nitrooxy)methyl]-1-piperidinyl]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 646510-52-3 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[4-[2-(nitrooxy)ethyl]-1-piperidinyl]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

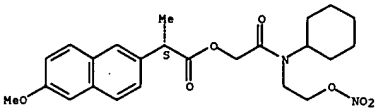
Absolute stereochemistry.



RN 646510-72-7 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[4-[2-(nitrooxy)ethyl]-1-piperazinyl]-2-oxoethyl ester, monohydrochloride, (αS)- (9CI) (CA INDEX NAME)

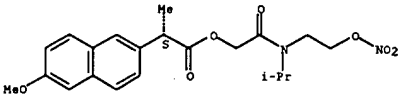
Absolute stereochemistry.

L10 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
Absolute stereochemistry.



IT 886458-12-4P, [N-Isopropyl-N-[2-(nitrooxy)ethyl]carbamoyl]methyl-[(2S)-2-[6-methoxy(2-naphthyl)propanoate 886458-15-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and antiinflammatory activity of substituted naproxen glycolamides)
RN 886458-12-4 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[(1-methylethyl)[2-(nitrooxy)ethyl]amino]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

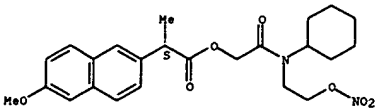


RN 886458-15-7 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[cyclohexyl[2-(nitrooxy)ethyl]amino]-2-oxoethyl ester, (αS)-, mononitrate (9CI) (CA INDEX NAME)

CM 1

CRN 886458-14-6
CMF C24 H30 N2 O7

Absolute stereochemistry.



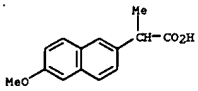
CM 2

CRN 7697-37-2
CMF H N O3

L10 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

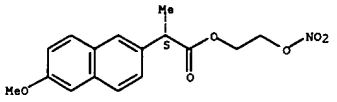
L10 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
NAME)



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:242101 CAPLUS
DN 140:417757
TI Pharmacological studies on nitro-naproxen (naproxen-2-nitrooxyethylester)
AU Jain, Naveen K.; Patil, Chandrashekhar S.; Kartasasmita, R. E.; Decker, M.; Lehmann, J.; Kulkarni, Shrinivas K.
CS Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, 160014, India
SO Drug Development Research (2004), 61(2), 66-78
CODEN: DDREDK; ISSN: 0272-4391
PB Wiley-Liss, Inc.
DT Journal
LA English
AB Naproxen-2-nitrooxyethylester (S-(+)-2-(6-methoxy-2-naphthyl)propanoic acid-2-nitrooxyethylester, LE-EK06) was synthesized from naproxen and 2-nitrooxyethylbromide as a novel nitric oxide-releasing derivative of naproxen. Molar equivalents of LE-EK06 (6.93-27.73 mg/kg, p.o.) to naproxen dose-dependently exhibited greater antinociceptive activity in comparison to naproxen in a writhing assay. The compound (5.54-22.18 mg/kg, p.o.) showed greater anti-inflammatory activity at 2 h after as comparable to its effect at 4 h after carrageenan challenge in rats. Further, LE-EK06 (9.45 mg/kg, p.o.) was more potent in the carrageenan-evoked hyperalgesia. LE-EK06 (11.09 mg/kg, p.o.) and naproxen (8.0 mg/kg, p.o.) showed a comparable inhibitory effect on exudate formation and migration of polymorphonuclear leukocytes (PMNs) in a carrageenan-induced pleurisy test. Further, the compound (11.09 mg/kg, p.o.) significantly reduced myeloperoxidase activity in carrageenan-treated paw and demonstrated significantly less gastrotoxicity in acute and chronic (21 days) studies. The SEM revealed that LE-EK06 showed only mild gastric damage (slight disruption of mucus layer) in comparison to naproxen. The present study suggested that naproxen-2-nitrooxyethylester (LE-EK06) represents a novel gastric sparing NSAID.
IT 693235-67-5P, LE-EK 06
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmacol. studies on nitro-naproxen)
RN 693235-67-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-(nitrooxy)ethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 23981-80-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmacol. studies on nitro-naproxen)
RN 23981-80-8 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl- (8CI, 9CI) (CA INDEX

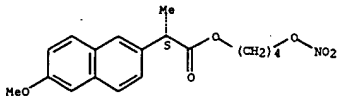
L10 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN APPLICANT
AN 2004:203791 CAPLUS
DN 140:253349
TI Process for preparing nitrooxyalkyl esters of naproxen and bromonaproxen.
IN Del Soldato, Piero; Santus, Giancarlo; Benedini, Francesca
PA. Nicox S.A., Fr.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004020384	A1	20040311	WO 2003-EP8698	20030806
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2497187	A1	20040311	CA 2003-2497187	20030806
	AU 2003266966	A1	20040319	AU 2003-266966	20030806
	EP 1532098	A1	20050525	EP 2003-747879	20030806
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	CN 1678560	A	20051005	CN 2003-820605	20030806
	JP 2005536558	T	20051202	JP 2004-532054	20030806
	NZ 537993	A	20061130	NZ 2003-537993	20030806
	ZA 2005000890	A	20060222	ZA 2005-890	20050131
	US 2006173005	A1	20060803	US 2005-523722	20050914
PRAI	IT 2002-MI1861	A	20020829		
	WO 2003-EP8698	W	20030806		

OS CASREACT 140:253349; MARPAT 140:253349
AB RCO2(CR1R2)m(CR3R4)n(CR5R6)oXp(CR7R8)q(CR9R10)r(CR11R12)sONO2 [R = naproxen, bromonaproxen residue; R1-R12 = H, alkyl, aralkyl; m, n, o, q, r, s = 0-6; p = 0, 1; X = O, S, SO, SO2, NR13, PR13, (substituted) cycloalkylene, arylene, heterocyclylene; R13 = H, alkyl], were prepared by reaction of RCO2Z (R as defined above; Z = H, Li+, Na+, K+, Ca++, Mg++, tetralkylammonium, tetralkylphosphonium) with Y(CR1R2)m(CR3R4)n(CR5R6)oXp(CR7R8)q(CR9R10)r(CR11R12)sONO2 [Y = halo, BF4, SbF6, FSO3, ASO3; A = (substituted) alkyl; other variables as defined above]. Thus, a mixture of naproxen and KHCO3 was heated in DMF at 50-60° for 90 min.; the mixture was cooled to room temperature and treated with KI and 4-bromobutyl nitrate (preparation given) followed by stirring for
25 h to give 73% naproxen 4-nitrooxybutyl ester.
IT 163133-43-5P, (S)-2-(6-Methoxy-2-naphthyl)propanoic acid 4-nitrooxybutyl ester 669692-80-2P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

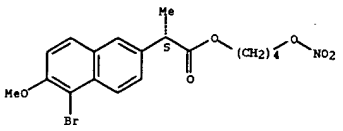
Absolute stereochemistry.

L10 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



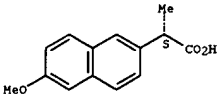
RN 669692-80-2 CAPLUS
CN 2-Naphthaleneacetic acid, 5-bromo-6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 22204-53-1, Naproxen 84236-26-0, (S)-2-(5-Bromo-6-methoxy-2-naphthyl)propanoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
RN 22204-53-1 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

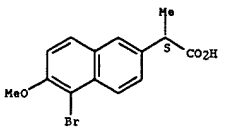
Absolute stereochemistry. Rotation (+).



RN 84236-26-0 CAPLUS
CN 2-Naphthaleneacetic acid, 5-bromo-6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L10 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

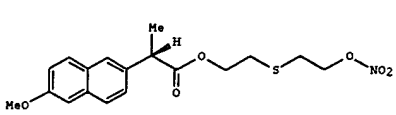


RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:41217 CAPLUS
DN 140:111135
TI Preparation of nitrosated nonsteroidal antiinflammatory compounds
IN Earl, Richard A.; Ezawa, Maiko; Fang, Xinqin; Garvey, David S.; Gaston, Ricky D.; Khanapure, Subhash P.; Letts, Gordon L.; Lin, Chia-En; Ranatunge, Ramani R.; Richardson, Stewart K.; Schroeder, Joseph D.; Stevenson, Cheri A.; Wey, Shiow-Jyi
PA Nitromed, Inc., USA
SO PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004004648	A2	20040115	WO 2003-US21026	20030703
	WO 2004004648	A3	20041028		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2491127	A1	20040115	CA 2003-2491127	20030703
	AU 2003247792	A1	20040123	AU 2003-247792	20030703
	US 2004024057	A1	20040205	US 2003-612014	20030703
	EP 1539729	A2	20050615	EP 2003-763193	20030703
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2005539089	T	20051222	JP 2004-562619	20030703
	US 2005222243	A1	20051006	US 2005-134358	20050523
PRAI	US 2002-393111P	P	20020703		
	US 2002-397979P	P	20020724		
	US 2002-418353P	P	20021016		
	US 2003-449798P	P	20030226		
	US 2003-456182P	P	20030321		
	US 2003-612014	A3	20030703		
	WO 2003-US21026	W	20030703		

OS MARPAT 140:111135
GI



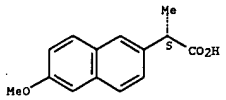
II

AB Title compds. RnRmHC-CO-X [Rm = H, alkyl; Rn = 4-((thiophen-2-yl)carbonyl)phenyl, 3-(benzoyl)phenyl, etc.; X = Y-alkyl-aryl, etc.; Y = O, S; I] are prepared For instance, naproxen is coupled to 2,2'-thiodiethanol (CH2Cl2, DMAP, EDCI) and treated with Ac2O/HNO3 at 0° to give II. I are nitrosated nonsteroidal antiinflammatory drugs (NSAIDs) used alone or are combined with one compd. that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase. The invention provides methods for treating inflammation, pain, fever, gastrointestinal disorders, etc.

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

IT 22204-53-1D, Naproxen, nitrosated derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination pharmaceutical; preparation of naproxen-derived nitrosated antiinflammatory compds.)
RN 22204-53-1 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

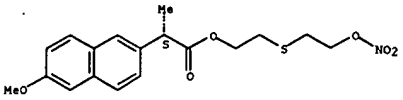


IT 646509-36-6P, 2-[[2-(Nitrooxy)ethyl]thio]ethyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646509-38-8P, 2-[[2-(Nitrooxy)ethyl]sulfonyl]ethyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646509-39-9P 646509-41-3P, [2-[[2-(Nitrooxy)ethyl](4-nitrophenyl)amino]ethyl] (2S)-2-[6-methoxy-2-naphthyl]propanoate 646509-43-5P, (2R)-2,3-Bis(nitrooxy)propyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646509-55-9P, [5-[(Nitrooxy)methyl]-1,3-dioxan-5-yl]methyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646509-59-3P, 2,2-Bis(nitrooxy)propyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646509-67-3P 646509-71-9P, 2-Nitro-3-(nitrooxy)-2-(nitrooxymethyl)propyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646509-88-8P, [N-Methyl-N-[2-(nitrooxy)ethyl]carbamoyl]methyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646509-94-6P, [N-Ethyl-N-[2-(nitrooxy)ethyl]carbamoyl]methyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646509-98-0P, 2-[4-(Nitrooxymethyl)piperidin-1-yl]-2-oxoethyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646510-12-5P, [[[2-(Nitrooxy)ethyl]oxy]carbonyl]methyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646510-15-8P, [N-[3-(Nitrooxy)propyl]carbamoyl]methyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646510-30-7P, (2S)-2-Hydroxy-3-(nitrooxy)propyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646510-37-4P, (2S)-2,3-Bis(nitrooxy)propyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646510-39-6P, (2R)-2-Hydroxy-3-(nitrooxy)propyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646510-52-3P, 2-[4-[2-(Nitrooxy)ethyl]piperidin-1-yl]-2-oxoethyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646510-62-5P, [N-Methyl-N-[3-(nitrooxy)propyl]carbamoyl]methyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646510-72-7P 646510-79-4P, 3-[[(2S)-2-(6-Methoxy-2-naphthyl)propanoyl]oxy]-2-methyl-2-[(nitrooxy)methyl]propyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646511-00-4P, 4-[[(2S)-2-(6-Methoxy-2-naphthyl)propanoyl]oxy] (2S,3S)-2,3-bis(nitrooxy)butyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646511-02-6P, [(2S,3S)-2,3-Bis(nitrooxy)-4-hydroxybutyl]

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
(2S)-2-[6-(methyloxy)-2-naphthyl]propanoate 646511-14-0P, (2R)-2-(Nitrooxy)-3-(phenylmethoxy)propyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646511-25-3P, 2-[[(4-Methylphenyl)sulfonyl][2-(nitrooxy)ethyl]amino]ethyl (2S)-2-(6-methoxy-2-naphthyl)propanoate 646511-47-9P, [[[2-(Nitrooxy)ethyl]oxy]carbonyl]methyl 2-(6-methoxy-2-naphthyl)propanoate 646511-48-0P, [N-[3-(Nitrooxy)propyl]carbamoyl]methyl 2-(6-methoxy-2-naphthyl)propanoate
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of naproxen-derived nitrosated antiinflammatory compds.)

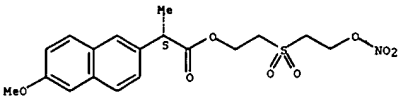
RN 646509-36-6 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[[2-(nitrooxy)ethyl]thio]ethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



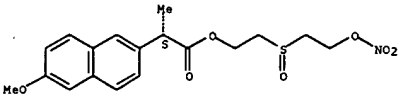
RN 646509-38-8 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[[2-(nitrooxy)ethyl]sulfonyl]ethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

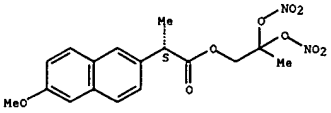


RN 646509-39-9 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[[2-(nitrooxy)ethyl]sulfinyl]ethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

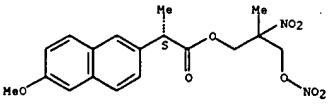


L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



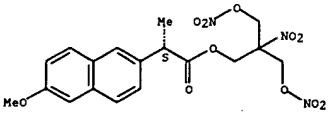
RN 646509-67-3 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-methyl-2-nitro-3-(nitrooxy)propyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



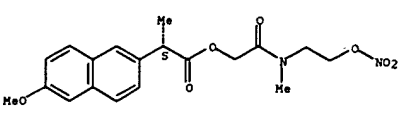
RN 646509-71-9 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-nitro-3-(nitrooxy)-2-[(nitrooxy)methyl]propyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 646509-88-8 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[methyl[2-(nitrooxy)ethyl]amino]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

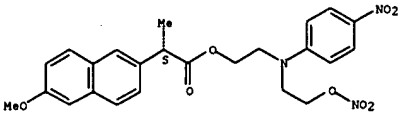


RN 646509-94-6 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[ethyl[2-(nitrooxy)ethyl]amino]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN . (Continued)

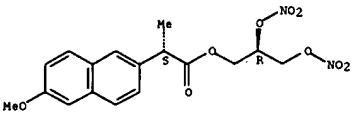
RN 646509-41-3 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[[2-(nitrooxy)ethyl](4-nitrophenyl)amino]ethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



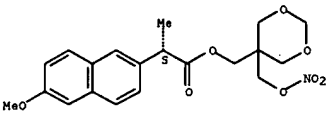
RN 646509-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (2R)-2,3-bis(nitrooxy)propyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 646509-55-9 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, [5-[(nitrooxy)methyl]-1,3-dioxan-5-yl]methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

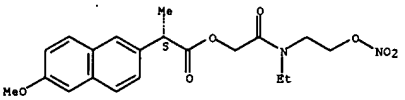


RN 646509-59-3 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2,2-bis(nitrooxy)propyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

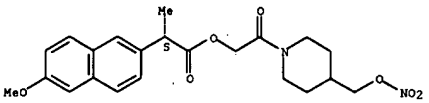
L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
NAME)

Absolute stereochemistry.



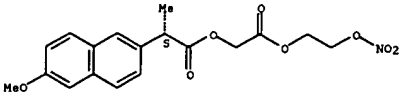
RN 646509-98-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[4-[(nitrooxy)methyl]-1-piperidinyl]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



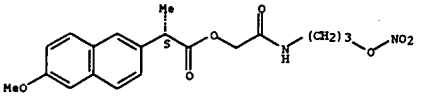
RN 646510-12-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[2-(nitrooxy)ethoxy]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



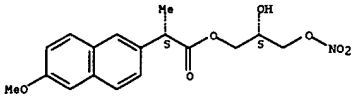
RN 646510-15-8 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[[3-(nitrooxy)propyl]amino]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



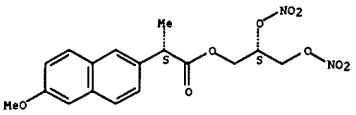
L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 646510-30-7 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (2S)-2-hydroxy-3-(nitrooxy)propyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



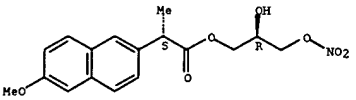
RN 646510-37-4 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (2S)-2,3-bis(nitrooxy)propyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 646510-39-6 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (2R)-2-hydroxy-3-(nitrooxy)propyl ester, (αS)- (9CI) (CA INDEX NAME)

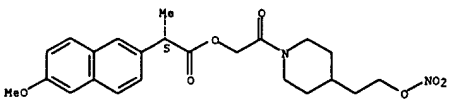
Absolute stereochemistry.



RN 646510-52-3 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[4-[2-(nitrooxy)ethyl]-1-piperidinyl]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

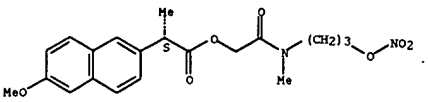
Absolute stereochemistry.

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



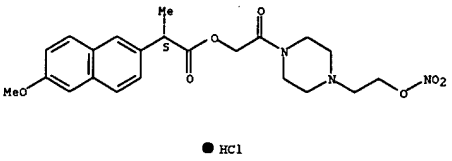
RN 646510-62-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[methyl[3-(nitrooxy)propyl]amino]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 646510-72-7 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[4-[2-(nitrooxy)ethyl]-1-piperazinyl]-2-oxoethyl ester, monohydrochloride, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



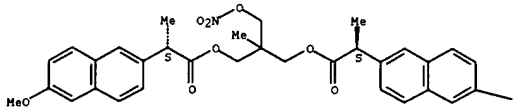
● HCl

RN 646510-79-4 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-methyl-2-[(nitrooxy)methyl]-1,3-propanediyl ester, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



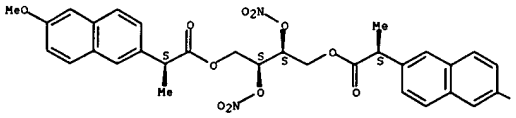
PAGE 1-B

OMe

RN 646511-00-4 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (2S,3S)-2,3-bis(nitrooxy)-1,4-butanediyl ester, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



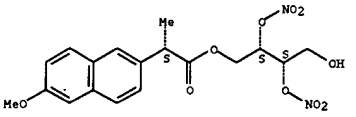
PAGE 1-B

OMe

RN 646511-02-6 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (2S,3S)-4-hydroxy-2,3-bis(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

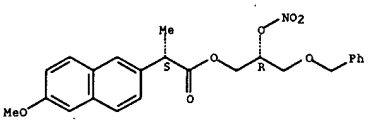
Absolute stereochemistry.

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



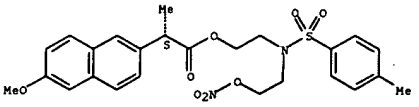
RN 646511-14-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (2R)-2-(nitrooxy)-3-(phenylmethoxy)propyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

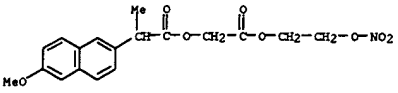


RN 646511-25-3 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[[(4-methylphenyl]sulfonyl][2-(nitrooxy)ethyl]amino]ethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

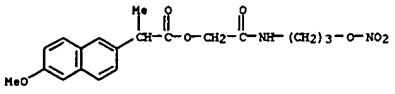


RN 646511-47-9 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[2-(nitrooxy)ethoxy]-2-oxoethyl ester (9CI) (CA INDEX NAME)



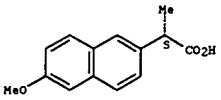
RN 646511-48-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[[3-(nitrooxy)propyl]amino]-2-oxoethyl ester (9CI) (CA INDEX NAME)

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



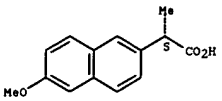
IT 22204-53-1 26159-34-2, (2S)-2-(6-Methoxy-2-naphthyl)propanoic acid sodium salt
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of naproxen-derived nitrosated antiinflammatory compds.)
RN 22204-53-1 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 26159-34-2 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

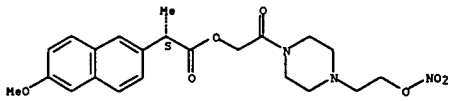


● Na

IT 646510-77-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of naproxen-derived nitrosated antiinflammatory compds.)
RN 646510-77-2 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 2-[4-[2-(nitrooxy)ethyl]-1-piperazinyl]-2-oxoethyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

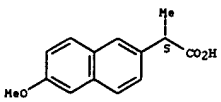


L10 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:2684 CAPLUS
DN 140:73178
TI Nitroxy derivatives of non-steroidal anti-inflammatory compounds as selective inhibitors of cyclooxygenase-2 for the treatment of inflammation
IN Del Soldato, Piero; Santus, Giancarlo
PA Nicox S.A., Fr.
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004000300	A1	20031231	WO 2003-EP6651	20030624
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IT 2002MI1399	A1	20031229	IT 2002-MI1399	20020625
AU 2003238042	A1	20040106	AU 2003-238042	20030624
PRAI IT 2002-MI1399	A	20020625		
WO 2003-EP6651	W	20030624		

OS MARPAT 140:73178
AB The present invention relates to compds. able to inhibit selectively the enzyme cyclooxygenase-2 (COX-2) without inhibiting substantially the enzyme COX-1. Specifically, the present invention concerns nitroxy derivs. of non-steroidal anti-inflammatory compds., which are able to inhibit selectively the enzyme COX-2. The compds. of the invention are useful in the treatment and/or prophylaxis of inflammatory processes.
IT 26159-34-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of methoxymethylnaphthalenacetic acid bromopropyl ester; nitroxy derivs. of non-steroidal anti-inflammatory compds. as selective inhibitors of cyclooxygenase-2 for treatment of inflammation)
RN 26159-34-2 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

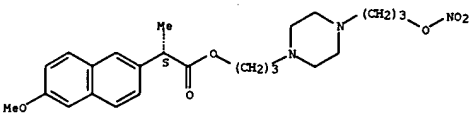


● Na

IT 639857-86-6P

L10 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of methoxymethylnaphthalenacetic acid nitrooxypropylpiperazinylpropyl ester dihydrochloride; nitroxy derivs. of non-steroidal anti-inflammatory compds. as selective inhibitors of cyclooxygenase-2 for treatment of inflammation)
RN 639857-86-6 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 3-[4-[3-(nitrooxy)propyl]-1-piperazinyl]propyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

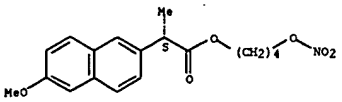
L10 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:434515 CAPLUS
DN 139:22023
TI Preparation of (S)-naproxen 4-nitrooxybutyl ester for treatment of pain
IN Belli, Aldo; Cannata, Vincenzo; Fonduca, Telly; Hedberg, Martin; Westermark, Andreas; Villa, Marco
PA Astrazeneca A.B., Swed.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003045896	A1	20030605	WO 2002-SE2184	20021126
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2465697	A1	20030605	CA 2002-2465697	20021126
	AU 2002365372	A1	20030610	AU 2002-365372	20021126
	EP 1451140	A1	20040901	EP 2002-791150	20021126
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2005510557	T	20050421	JP 2003-547348	20021126
	US 2005234123	A1	20051020	US 2005-497012	20050609
PRAI	SE 2001-3978	A	20011127		
	WO 2002-SE2184	W	20021126		

OS CASREACT 139:22023; MARPAT 139:22023
AB The present invention relates to a new process for the preparation of the (S)-naproxen 4-nitrooxybutyl ester and to new intermediates obtained and used therein. The invention further relates to the use of the new intermediates for the manufacturing of pharmaceutically active compds. such as (S)-naproxen 4-nitrooxybutyl ester. The invention also relates to the use of (S)-naproxen 4-nitrooxybutyl ester prepared according to the process of the present invention for the manufacturing of a medicament for the treatment of pain.
IT 163133-43-5P
RL: IMF (Industrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (S)-naproxen 4-nitrooxybutyl ester for treatment of pain)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

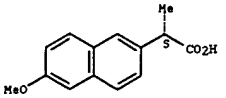
Absolute stereochemistry.

L10 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



IT 22204-53-1, (S)-Naproxen
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of (S)-naproxen 4-nitrooxybutyl ester for treatment of pain)
RN 22204-53-1 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

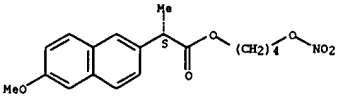
L10 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:115100 CAPLUS
DN 134:178355
TI Process for the preparation of naproxene nitroxyalkyl esters
IN Benedini, Francesca; Oldani, Erminio; Castaldi, Graziano; Tarquini, Antonio
PA Nicox S.A., Fr.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001010814	A1	20010215	WO 2000-EP7222	20000727
	W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2380116	A1	20010215	CA 2000-2380116	20000727
	EP 1200386	A1	20020502	EP 2000-951456	20000727
	EP 1200386	B1	20031001		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	TR 200200290	T2	20020521	TR 2002-290	20000727
	BR 2000012915	A	20020604	BR 2000-12915	20000727
	HU 200202435	A2	20021128	HU 2002-2435	20000727
	JP 2003506425	T	20030218	JP 2001-515282	20000727
	AT 251109	T	20031015	AT 2000-951456	20000727
	EP 1384707	A1	20040128	EP 2003-102132	20000727
	EP 1384707	B1	20050608		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, FI, CY				
	PT 1200386	T	20040227	PT 2000-951456	20000727
	ES 2208390	T3	20040616	ES 2000-951456	20000727
	AU 778694	B2	20041216	AU 2000-64385	20000727
	RU 2248348	C2	20050320	RU 2002-102860	20000727
	AT 297372	T	20050615	AT 2003-102132	20000727
	ES 2243859	T3	20051201	ES 2003-3102132	20000727
	ZA 2002000478	A	20030818	ZA 2002-478	20020118
	US 6700011	B1	20040302	US 2002-31412	20020118
	NO 2002000515	A	20020201	NO 2002-515	20020201
	ZA 2003004525	A	20040211	ZA 2003-4525	20030610
	US 2005119339	A1	20050602	US 2003-625558	20030724
PRAI	IT 1999-MI1753	A	19990804		
	EP 2000-951456	A3	20000727		
	WO 2000-EP7222	W	20000727		
	US 2002-31412	A3	20020118		

OS CASREACT 134:178355; MARPAT 134:178355
AB A process for obtaining nitroxyalkyl esters of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, was characterized in that a halide of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO2, wherein Y is a C2-C20 alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as defined containing a cycloalkylene as defined, in the presence of an inorg. base. E.g., to a solution of 4-nitroxybutan-1-ol and K2CO3 in dichloromethane is added 2-(S)-(6-methoxy-2-naphthyl)propanoic acid chloride. to give the 4-nitroxybutyl ester of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (85%, ee 98%).
IT 163133-43-5P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of naproxene nitroxyalkyl esters)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

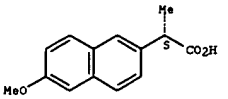
Absolute stereochemistry.

L10 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



IT 22204-53-1, Naproxen
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of naproxene nitroxyalkyl esters)
RN 22204-53-1 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

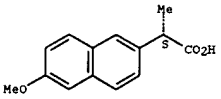
L10 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2000:628123 CAPLUS
DN 133:207818
TI Preparation of nitroxymethylpyridines and related compounds having antiinflammatory, analgesic and antithrombotic activity
IN Benedini, Francesca; Del Soldato, Piero
PA Nicox S.A., Fr.
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051988	A1	20000908	WO 2000-EP1454	20000223
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	IT 1308633	B1	20020109	IT 1999-MI413	19990302
	CA 2361164	A1	20000908	CA 2000-2361164	20000223
	EP 1154999	A1	20011121	EP 2000-909234	20000223
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	BR 2000008582	A	20020213	BR 2000-8582	20000223
	HU 200200386	A2	20020629	HU 2002-386	20000223
	JP 2002538142	T	20021112	JP 2000-602215	20000223
	AU 770642	B2	20040226	AU 2000-31588	20000223
	RU 2240997	C2	20041127	RU 2001-124271	20000223
	ZA 2001006650	A	20021113	ZA 2001-6650	20010813
	US 6613784	B1	20030902	US 2001-926095	20010830
PRAI	IT 1999-MI413	A	19990302		
	WO 2000-EP1454	W	20000223		

OS MARPAT 133:207818
AB Organic or inorg. salts of AX1N(O)z [A = R(COXu)t; t = 0, 1; u = 0, 1; X = O, NH, NR1c; R1c = alkyl; R = specified aryl moiety; X1 = (CR1R2)aY(CR3R4)bO; R1-R4 = H, alkyl; a = 0-3; b = 1-3; Y = (aromatic) ring containing ≥1 salifiable N atom], were prepared Thus, 2-acetylbenzoic acid 6-chloromethyl-2-methylpyridinyl ester (preparation given) was heated with AgNO3 in MeCN at 80° for 30 h to give 2-acetylbenzoic acid 6-nitroxymethyl-2-methylpyridinyl ester. The HCl salt of the latter (NCX 4050) at 10-5 M gave 80% inhibition of rabbit aorta contraction.
IT 290335-25-0P 290335-27-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitroxymethylpyridines and related compds. having antiinflammatory, analgesic and antithrombotic activity)
RN 290335-25-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, [6-[(nitrooxy)methyl]-2-pyridinyl]methyl ester, monohydrochloride, (αS)- (9CI) (CA INDEX NAME)

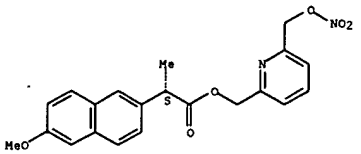
L10 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of nitroxymethylpyridines and related compds. having antiinflammatory, analgesic and antithrombotic activity)
RN 22204-53-1 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
Absolute stereochemistry.



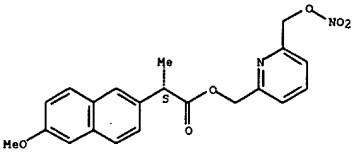
● HCl

RN 290335-27-2 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, [6-[(nitrooxy)methyl]-2-pyridinyl]methyl ester, (αS)-, mononitrate (9CI) (CA INDEX NAME)

CM 1

CRN 290335-26-1
CMF C21 H20 N2 O6

Absolute stereochemistry.



CM 2

CRN 7697-37-2
CMF H N O3

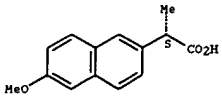
IT 22204-53-1

L10 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1998:221441 CAPLUS
DN 128:226234
TI Nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their preparing method and use
IN Cai, Xiong; Qian, Changgeng
PA Cai, Xiong, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 22 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 1144092	A	19970305	CN 1995-109791	19950825
PRAI	CN 1995-109791		19950825		

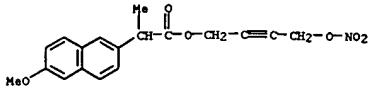
AB The present invention provides a group of nonsteroidal anti-inflammatory drugs (NSAID) capable of releasing nitric oxide and their nitrates. The NSAID include aspirin, indomethacin, naproxen, brufen, pirprofen, phenol pirprofen, flurbiprofen, ketoprofen, and diclofenac sodium and can be extensively used as antipyretics, analgesics, and antiinflammatory for prevention and treatment of angiocardiopathy and cerebrovascular diseases. The new NSAID nitrates can release nitric oxide in vivo and can reduce the toxicity of NSAID on the digestive tract.
IT 22204-53-1, Naproxen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their preparing method and use)
RN 22204-53-1 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 204633-04-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their preparing method and use)
RN 204633-04-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)-2-butynyl ester (9CI) (CA INDEX NAME)

L10 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



L10 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

AN 1995:667266 CAPLUS

DN 123:82961

TI Preparation of organic nitrate esters having antiinflammatory and/or analgesic activity

IN Del Soldato, Piero

PA Nicox Ltd., Ire.

SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

DT Patent

LA English

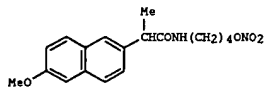
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9509831	A1	19950413	WO 1994-EP3182	19940923
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	GB 2283238	A	19950503	GB 1993-20599	19931006
	GB 2283238	B	19971126		
	CA 2173582	A1	19950413	CA 1994-2173582	19940923
	CA 2173582	C	20061128		
	AU 9478092	A	19950501	AU 1994-78092	19940923
	AU 678063	B2	19970515		
	EP 722434	A1	19960724	EP 1994-928801	19940923
	EP 722434	B1	19980729		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
	HU 74446	A2	19961230	HU 1996-874	19940923
	HU 218923	B	20001228		
	BR 9407749	A	19970212	BR 1994-7749	19940923
	JP 09503214	T	19970331	JP 1994-510585	19940923
	AT 168986	T	19980815	AT 1994-928801	19940923
	ES 2120070	T3	19981016	ES 1994-928801	19940923
	RU 2136653	C1	19990910	RU 1996-108907	19940923
	JP 3775796	B2	20060517	JP 1995-510585	19940923
	US 5700947	A	19971223	US 1996-624508	19960405
	US 5780495	A	19980714	US 1997-902570	19970729
PRAI	GB 1993-20599	A	19931006		
	IT 1994-MI916	A	19940510		
	WO 1994-EP3182	W	19940923		
	US 1996-624508	A3	19960405		

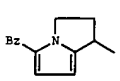
OS CASREACT 123:82961; MARPAT 123:82961

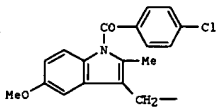
GI

L10 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



I

Q1= 

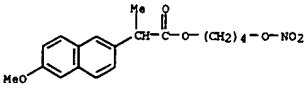
Q2= 

AB The title compds. MCOY[C(A)(B)]nONO2 [A, B = H, (un)branched alkyl; M = Q1, Q2, 2-(6-methoxy)naphthyl, etc.; n = 1-10], useful as analgesics, antiinflammatory agents, and blood platelet aggregation inhibitors, are prepared Thus, 2-(6-methoxy-2-naphthyl)propionic acid was converted into its Na carboxylate salt with NaOEt, the salt condensed with 1-bromo-4-chlorobutane, and the 4-chlorobutyl 2-(6-methoxy-2-naphthyl)propionate intermediate nitrated by reaction with AgNO3, producing the 4-nitratobutyl ester, II.

IT 170591-17-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of organic nitrate esters having antiinflammatory and/or analgesic activity)

RN 170591-17-0 CAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

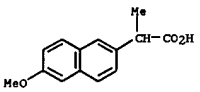


IT 23981-80-8, 2-(6-Methoxy-2-naphthyl)propionic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of organic nitrate esters having antiinflammatory and/or analgesic activity from)

RN 23981-80-8 CAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl- (8CI, 9CI) (CA INDEX NAME)

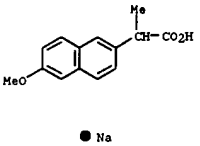
L10 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



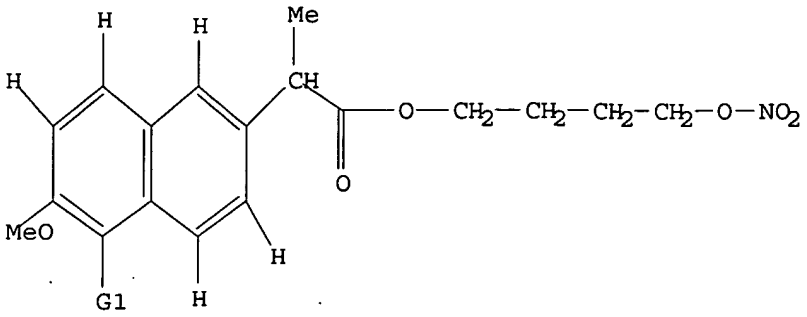
IT 55577-80-5P, Sodium 2-(6-methoxy-2-naphthyl)propionate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of organic nitrate esters having antiinflammatory and/or analgesic activity from)

RN 55577-80-5 CAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt (9CI) (CA INDEX NAME)



=> => d que l14 stat
L11 STR



G1 H,Br

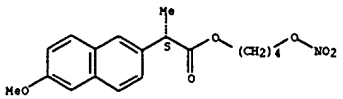
Structure attributes must be viewed using STN Express query preparation.
L13 3 SEA FILE=REGISTRY SSS FUL L11
L14 46 SEA FILE=CAPLUS ABB=ON PLU=ON L13

=> d 1-46 bib abs hitstr

L14 ANSWER 1 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:366031 CAPLUS
DN 145:327992
TI Nitric oxide and prostacyclin pathways: an integrated mechanism that limits myocardial infarction progression in anesthetized rats
AU Rossoni, Giuseppe; Manfredi, Barbara; De Gennaro Colonna, Vito; Brini, Anna Teresa; Polvani, Gianluca; Clement, Maria Giovanna; Berti, Ferruccio
CS Department of Pharmacological Sciences, University of Milan, Milan, 20133, Italy
SO Pharmacological Research (2006), 53(4), 359-366
CODEN: PHMREP; ISSN: 1043-6618
PB Elsevier B.V.
DT Journal
LA English
AB Nitric oxide (NO) and cyclooxygenase-derived prostaglandins, such as prostacyclin (PGI2), are involved in vascular homeostasis. To better understand the reciprocal role of both NO and PGI2 on myocardial infarction in the rat, we have investigated the cardioprotective effect of nitro-naproxen, isosorbide dinitrate (ISDN), L-arginine, defibrotide and naproxen. In this study, male Wistar rats were treated orally once a day for 5 consecutive days with the compds. under investigation and then, under anesthesia, the animals were subjected to acute myocardial ischemia (30 min) and reperfusion (120 min). Systemic blood pressure, left ventricular pressure and related parameters of cardiac mechanics were recorded. Ventricular arrhythmias and infarct size of the left ventricular wall were also evaluated. Furthermore, cardiac myeloperoxidase (MPO) and plasma creatine phosphokinase (CPK) activities were determined Defibrotide, nitro-naproxen, ISDN and L-arginine all provided
a cardioprotection characterized by significant prevention of arrhythmias with high survival rate of the rats. Infarct size restriction was paralleled by reduction of both cardiac MPO and plasma CK. Cardioprotection of nitro-naproxen, ISDN and L-arginine involve nitrites/nitrates and PGI2-increased in the circulation associated to a reduction of thromboxane B2
(TXB2) in the blood. Defibrotide displays a cardioprotection by increasing PGI2 release and by reducing TXB2 in the blood. Naproxen was devoid a lower protecting activity on myocardial infarction, and PGI2 inhibition may have played a critical role in this context. The results suggested that the increase of both NO and PGI2 brings about a cascade of integrated cellular and mol. events which are of paramount importance in prevention of myocardial ischemic insult.
IT 163133-43-5, Nitro-naproxen
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitro-naproxen reduced blood thromboxane B2 and increased nitric oxide but not showed any effect on prostacyclin level in anesthetized rat)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

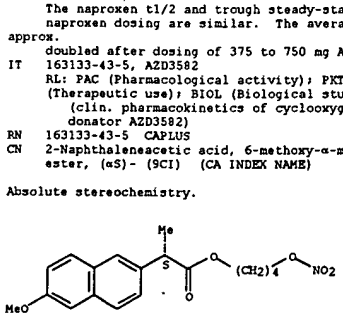
L14 ANSWER 1 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:226494 CAPLUS
DN 144:403727
TI Clinical pharmacokinetics of the cyclooxygenase inhibiting nitric oxide donator (CINOD) AZD3582
AU Fagerholm, Urban; Bjoernsson, Marcus A.
CS Clinical Pharmacology, AstraZeneca R and D Soedertaelje, Soedertaelje, S-151 85, Swed.
SO Journal of Pharmacy and Pharmacology (2005), 57(12), 1539-1554
CODEN: JPPMAB; ISSN: 0022-3573
PB Pharmaceutical Press
DT Journal
LA English
AB The clin. pharmacokinetics of the COX-inhibiting nitric oxide donator (CINOD) AZD3582 and its metabolites, including naproxen, NO, and nitrate, are summarized. AZD3582 has low aqueous solubility, moderate and passive intestinal permeability and is degraded by intestinal esterases. Its oral bioavailability (F) appears to be maximally a few per cent, and increases by several-fold after food intake. Ninety-four per cent or more of an AZD3582 dose is absorbed, of which at least 9-20% appears to be taken up as intact substance. AZD3582 has a predicted blood plasma protein binding degree of .apprx. 0.1%, a half-life (t1/2) of 3 to 10 h and does not accumulate after repeated once- and twice-daily dosing. In patients AZD3582 does not provide a significantly better gastrointestinal (GI) side-effect profile than the highly permeable and locally irritating naproxen. Possible reasons for this include considerable GI uptake as naproxen, limited duration and extent of NO donation in the GI mucosa and the circulation, tolerance development (involving auto-inhibition of NO catalyzing enzymes) and mucosal damage caused by NO. Blood pressure data suggest that NO is mainly donated within 3 h. The uptake of naproxen is slightly slower and lower (≥ 94% relative GI uptake and 80-85% relative F) after AZD3582 administration compared with naproxen dosing. The naproxen t1/2 and trough steady-state concns. after AZD3582 and naproxen dosing are similar. The average systemic nitrate exposure is approx.
doubled after dosing of 375 to 750 mg AZD3582 twice daily.
IT 163133-43-5, AZD3582
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. pharmacokinetics of cyclooxygenase inhibiting nitric oxide donator AZD3582)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

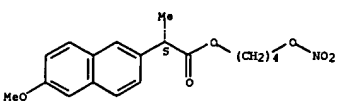
Absolute stereochemistry.



RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:173746 CAPLUS
DN 145:180218
TI Dose-effect comparisons of the CINOD AZD3582 and naproxen on upper gastrointestinal tract mucosal injury in healthy subjects
AU Wilder-Smith, Clive H.; Jonzon, Bror; Fornstedt-Wallin, Bodil; Hedman, Ann; Karlsson, Paer
CS Brain-Gut Research Group, Gastroenterology Group Practice, Bern, Switz.
SO Scandinavian Journal of Gastroenterology (2006), 41(3), 264-273
CODEN: SJGRA4; ISSN: 0036-5521
PB Taylor & Francis
DT Journal
LA English
AB Objective: The objective of this endoscopic study was to compare the effects on the gastroduodenal mucosa of healthy volunteers of different doses and dosing regimens of AZD3582, a cyclooxygenase-inhibiting nitric oxide donator (CINOD), with equimolar doses of naproxen. Material and methods: Healthy volunteers were enrolled in a single-center, randomized, double-blind, crossover trial consisting of two 12-day treatment periods and employing six sequences. The groups were: AZD3582 750 mg daily vs. 375 mg twice daily (n = 25), AZD3582 375 mg twice daily vs. 750 mg twice daily (n = 25) and naproxen 250 mg twice daily vs. 500 mg twice daily (n = 25). Results: Gastroduodenal tract damage was similar with AZD3582 375 mg twice daily and 750 mg twice daily (mean number of erosions and ulcers ±SD: 2.88 ± 3.95 vs. 3.08 ± 2.80, resp.; p = 0.824; 1 ulcer counted as 10 erosions). There was an indication of decreased gastroduodenal toxicity with AZD3582 750 mg daily compared with 375 mg twice daily (0.92 ± 2.08 vs. 2.71 ± 4.75, resp.; p = 0.068). Gastroduodenal toxicity was significantly lower with AZD3582 375 mg twice daily than with naproxen 250 mg twice daily (2.88 ± 3.95 vs. 6.16 ± 9.36; p < 0.05), and with AZD3582 750 mg twice daily vs. naproxen 500 mg twice daily (3.08 ± 2.80 vs. 6.68 ± 6.97; p < 0.05). Equimolar twice-daily doses of AZD3582 and naproxen resulted in similar naproxen plasma levels and serum thromboxane B2 inhibition. Conclusions: AZD3582 has an improved gastroduodenal safety profile compared with equimolar doses of naproxen. The gastroduodenal effects of AZD3582 375 mg and AZD3582 750 mg twice daily are similar. A once-daily regimen of AZD3582 might be less gastrotoxic than a twice-daily regimen.
IT 163133-43-5, AZD3582
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(administration of cyclooxygenase-inhibiting nitric oxide donator AZD3582 750mg daily once showed significantly less gastroduodenal mucosal damage compared to AZD3582 375mg twice daily and naproxen in healthy patient)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

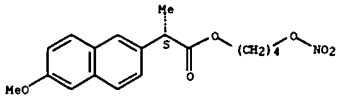


RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD

L14 ANSWER 3 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
ALL CITATIONS AVAILABLE IN THE RE FORMAT

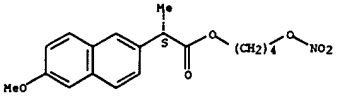
L14 ANSWER 4 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:85668 CAPLUS
DN 144:305060
TI A comparison of the cyclooxygenase inhibitor-NO donors (CINOD), NMI-1182 and AZD3582, using in vitro biochemical and pharmacological methods. [Erratum to document cited in CA143:379745]
AU Young, Delano V.; Cochran, Edward D.; Dhawan, Vijay; Earl, Richard A.; Ellis, James L.; Garvey, David S.; Janero, David R.; Khanapure, Subhash P.; Letts, L. Gordon; Melim, Terry L.; Murty, Madhavi G.; Shumway, Matthew J.; Wey, Shiow-Jyi; Zemtseva, Irina S.; Selig, William M.
CS Department of Biology, NitroMed Inc., Lexington, MA, 02421, USA
SO Biochemical Pharmacology (2006), 71(5), 711
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier B.V.
DT Journal
LA English
AB The x-axis of Figure 11 shown on p. 1349 should read "Incubation Time (min)". The corrected figure is given.
IT 163133-43-5, AZD3582
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison of cyclooxygenase inhibitor-NO donors (CINOD) NMI-1182 and AZD3582 using in vitro biochem. and pharmacol. methods in relation to naproxen release (Erratum))
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 5 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:46117 CAPLUS
DN 144:480639
TI Comparison of the COX-inhibiting nitric oxide donator AZD3582 and rofecoxib in treating the signs and symptoms of osteoarthritis of the knee
AU Schnitzer, Thomas J.; Kivitz, Alan J.; Lipetz, Robert S.; Sanders, Nicki Hee, Angela
CS Northwestern Center for Clinical Research, Chicago, IL, USA
SO Arthritis Care & Research (2005), 53(6), 827-837
CODEN: ARCREG; ISSN: 0893-7524
PB John Wiley & Sons, Inc.
DT Journal
LA English
AB Objective: To compare the efficacy, safety, and tolerability of AZD3582 with that of rofecoxib, naproxen, and placebo in patients with osteoarthritis (OA) of the knee, and to define the dosage of AZD3582 (125 mg, 375 mg, and 750 mg twice a day) that is noninferior in efficacy to rofecoxib. Methods: A double-blind study of 672 patients with OA of the knee was conducted. Patients who experienced increased pain on withdrawal of analgesia were randomized to receive AZD3582 125 mg, 375 mg, or 750 mg twice a day; rofecoxib 25 mg once a day; naproxen 500 mg twice a day; or placebo for 6 wk. Efficacy, tolerability, and safety were monitored throughout the study. The primary variable was the change in Western Ontario and McMaster Universities Osteoarthritis Index pain subscale from baseline to the mean of weeks 4 and 6, comparing AZD3582 with placebo for superiority and with rofecoxib for noninferiority using a predefined margin of 10 mm. Results: For the primary variable, AZD3582 375 mg and 750 mg were superior to placebo (least squares mean difference [95% confidence interval] -12 mm [-18, -6], P < 0.001 and -13 mm [-19, -7], P < 0.001, resp.) and were noninferior to rofecoxib (-2 mm [-8, 4], P < 0.001 and -3 mm [-9, 3], P < 0.001, resp.). AZD3582 125 mg was not significantly different from placebo for the primary variable. Conclusion: AZD3582 375 mg and 750 mg twice a day were superior to placebo and as effective as rofecoxib 25 mg/day in treating the signs and symptoms of OA of the knee. AZD3582 125 mg twice a day was not statistically different from placebo.
IT 163133-43-5, AZD3582
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase inhibiting nitric oxide donator AZD3582 was as effective as rofecoxib in treating signs and symptoms of osteoarthritis of knee in patient)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

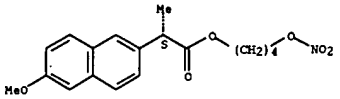
L14 ANSWER 6 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1354712 CAPLUS
DN 144:94350
TI A method of improving the medical treatment of pain
IN Christgau, Stephan; Hansen, Christian; Nilsson, Henrik
PA Osteologix A/S, Den.
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005123192	A2	20051229	WO 2005-DK401	20050617
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2006122274	A1	20060608	US 2005-269289	20051107
	WO 2006089546	A1	20060831	WO 2005-DK710	20051107
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
PRAI	DK 2004-947	A	20040617		
	DK 2003-691	A	20030507		
	DK 2003-932	A	20030620		
	DK 2003-1820	A	20031209		
	US 2003-528442P	P	20031209		
	WO 2004-DK328	A2	20040506		
	WO 2005-DK140	A2	20050228		
	WO 2005-DK401	A2	20050617		
	WO 2005-DK404	A2	20050617		

AB Methods for improving pain management in a mammal, the methods comprising administering a combination of a strontium-containing compound and a second therapeutically and/or prophylactically active substance selected from the group consisting of analgesic agents, anti-inflammatory agents and palliative agents to the mammal. Pharmaceutical compns. for use in such methods, comprising a strontium-containing compound and a second therapeutically
and/or prophylactically active substance selected from the group consisting of analgesic agents, anti-inflammatory agents and palliative agents. For example, a tablet containing naproxen 250, strontium malonate 210, lactose 100, corn starch 30, and magnesium stearate 10 mg was formulated.

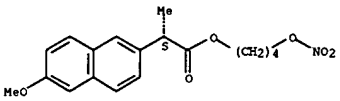
L14 ANSWER 6 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
IT 163133-43-5, HCT3012
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AZD3582; method of improving medical treatment of pain by administering combination of strontium-containing compound and second active substance)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 7 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1291302 CAPLUS
DN 145:431878
TI NMI-1182, a gastro-protective cyclo-oxygenase-inhibiting nitric oxide donor
AU Ellis, James L.; Augustyniak, Michael E.; Cochran, Edward D.; Earl, Richard A.; Garvey, David S.; Gordon, Laura J.; Janero, David R.; Khanapure, Subhash P.; Letts, L. Gordon; Melim, Terry L.; Murty, Madhavi G.; Schwalb, David J.; Shumway, Matthew J.; Selig, William M.; Trocha, A. Mark; Young, Delano V.; Zemtseva, Irina S.
CS NitroMed Inc., Lexington, MA, 02421-0781, USA
SO Inflammopharmacology (2005), 12(5-6), 521-534
CODEN: IAOAES; ISSN: 0925-4692
PB VSP
DT Journal
LA English
AB Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat inflammation and to provide pain relief but suffer from a major liability concerning their propensity to cause gastric damage. As nitric oxide (NO) is known to be gastro-protective we have synthesized a NO-donating prodrug of naproxen named NMI-1182. We evaluated two cyclo-oxygenase (COX)-inhibiting nitric oxide donors (CINODs), NMI-1182 and AZD3582, for their ability to be gastro-protective compared to naproxen and for their anti-inflammatory activity. NMI-1182 and AZD3582 were found to produce similar inhibition of COX activity to that produced by naproxen. Both NMI-1182 and AZD3582 produced significantly less gastric lesions after oral administration than naproxen. All three compds. effectively inhibited paw swelling in the rat carrageenan paw edema model. In the carrageenan air pouch model all three compds. significantly reduced PGE2 levels in the pouch exudate but only NMI-1182 and naproxen inhibited leukocyte influx. These data demonstrate that NMI-1182 has comparable anti-inflammatory activity to naproxen but with a much reduced likelihood to cause gastric damage.
IT 163133-43-5, AZD3582
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AZD3582 inhibited paw swelling and significantly decreased lesion formation in rat Carrageenan paw edema and gastric injury model resp.)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

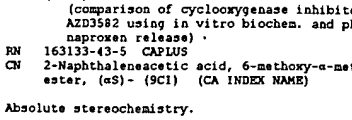
Absolute stereochemistry.



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1060180 CAPLUS
DN 143:379745
TI A comparison of the cyclooxygenase inhibitor-NO donors (CINOD), NMI-1182 and AZD3582, using in vitro biochemical and pharmacological methods
AU Young, Delano V.; Cochran, Edward D.; Dhawan, Vijay; Earl, Richard A.; Ellis, James L.; Garvey, David S.; Janero, David R.; Khanapure, Subhash P.; Letts, L. Gordon; Melim, Terry L.; Murty, Madhavi G.; Shumway, Matthew J.; Wey, Shiow-Jyi; Zemtseva, Irina S.; Selig, William M.
CS Departments of Biology, Lexington, MA, 02421, USA
SO Biochemical Pharmacology (2005), 70(9), 1343-1351
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier B.V.
DT Journal
LA English
AB Cyclooxygenase (COX, EC 1.14.99.1) inhibitor-nitric oxide (NO) donor (CINOD) hybrid compds. represent an attractive alternative to NSAID and coxib therapy. This report compares two CINODs, NMI-1182 (naproxen-glyceryl dinitrate) and AZD3582 (naproxen-Bu nitrate), for their ability to inhibit COX-1 and -2, deliver bioavailable nitric oxide, and release naproxen, using in vitro biochem. and pharmacol. methods. In human whole blood, both CINODs showed inhibition, comparable to naproxen, of both COX isoenzymes and slowly released naproxen. Both CINODs donated bioavailable NO, as detected by cGMP induction in the pig kidney transformed cell line, LLC-PK1, but NMI-1182 was more potent by 30-100 times than AZD3582, GTN, GDN, and ISDN and considerably faster in inducing cGMP synthesis than AZD3582. The nitrate groups of GTN, NMI-1182, and AZD3582 appeared to be bioactivated via a common pathway, since each compound desensitized LLC-PK1 cells to subsequent challenge with the other compds. Similar cGMP induction also occurred in normal, untransformed cells (human renal proximal tubule epithelial cells and hepatocytes from man, rat, and monkey); again, NMI-1182 was superior to AZD3582. NMI-1182 was also the more metabolically labile compound, releasing more absolute nitrate and nitrite (total NOx) in human stomach (in which NO is salutary) and liver S9 homogenates. Naproxen was also more rapidly freed from NMI-1182 than AZD3582 in human stomach, although liver S9 hydrolyzed both CINODs with similar rates. These in vitro tests revealed that NMI-1182 may be a better CINOD than AZD3582 because of its superior NO donating and naproxen liberating properties.
IT 163133-43-5, AZD3582
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison of cyclooxygenase inhibitor-NO donors (CINOD) NMI-1182 and AZD3582 using in vitro biochem. and pharmacol. methods in relation to naproxen release)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



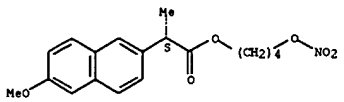
L14 ANSWER 8 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:571238 CAPLUS
DN 143:146164
TI Direct gas measurements indicate that the novel cyclooxygenase inhibitor AZD3582 is an effective nitric oxide donor in vivo
AU Adding, L. Christofer; Agvald, Per; Andersson, Lars I.; Jonzon, Bror; Hoogstraate, Janet; Gustafsson, Lars E.
CS Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, SE-171 77, Swed.
SO British Journal of Pharmacology (2005), 145(5), 679-687
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB AZD3582 [4-(nitrooxy)butyl-(2S)-2-(6-methoxy-2-naphthyl)propanoate] is a COX-inhibiting nitric oxide donor that inhibits COX-1 and COX-2. It is as effective as naproxen in models of pain and inflammation, but causes less gastroduodenal damage. Nitric oxide (NO) is generated from AZD3582 in vitro, and this study sought to show that the drug donates NO in vivo. In anesthetized male New Zealand white rabbits, the endogenous NO concentration in exhaled air was reduced by NG-nitro-L-arginine Me ester (L-NAME) (30 mg kg-1 i.v.) from 33.5±1.0 ppb (means±s.e.m.; n = 5 per group) to 3.0±1.0 ppb, while increasing blood pressure and reducing heart rate. AZD3582 (0.2, 0.6, 2.0 or 6.0 μmol kg-1 min-1) given 30 min after L-NAME increased the concentration of NO in exhaled air (P < 0.05), decreased blood pressure and increased heart rate in a dose-dependent manner vs. L-NAME control values. The peak mean NO concentration obtained was 44±8.0 ppb. In in situ-perfused rabbit lungs, L-NAME (185 μmol l-1) reduced the NO concentration in exhaled air from 106±13 to 4.0±0.4 ppb (n = 5). Addition of AZD3582 (6 μmol min-1) to the perfusate produced an initial rapid increase in the NO concentration in exhaled air, followed by a sustained, but lower plateau. Infusion of L-NAME increased, and AZD3582 decreased, pulmonary arterial pressure. In both anesthetized rabbits and in the perfused lungs, brief periods of hypoxia increased NO concns. generated by AZD3582. We conclude that, in rabbits, AZD3582 donates NO in vivo with characteristics similar to those reported for nitroglycerin and isosorbide nitrates.
IT 163133-43-5, AZD3582
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase inhibitor AZD3582 is effective nitric oxide donor)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

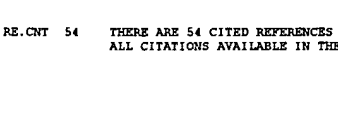
L14 ANSWER 9 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:465142 CAPLUS
DN 143:206318
TI AZD3582 increases heme oxygenase-1 expression and antioxidant activity in vascular endothelial and gastric mucosal cells
AU Berndt, Georg; Grosser, Nina; Hoogstraate, Janet; Schroeder, Henning
CS School of Pharmacy, Department of Pharmacology and Toxicology, Martin Luther University, Halle (Saale), 06099, Germany
SO European Journal of Pharmaceutical Sciences (2005), 25(2-3), 229-235
CODEN: EPSCED; ISSN: 0928-0987
PB Elsevier B.V.
DT Journal
LA English
AB AZD3582 [4-(nitrooxy)-butyl-(2S)-2-(6-methoxy-2-naphthyl)-propanoate] is a COX-inhibiting nitric oxide donor (CINOD). Incubation of human endothelial cells (derived from umbilical cord) with AZD3582 (10-100 μM) led to increased expression of heme oxygenase (HO)-1 mRNA and protein. Heme oxygenase-1 (HO-1) is a crucial mediator of antioxidant and tissue-protective actions. In contrast, naproxen (a non-selective NSAID) and rofecoxib (a selective inhibitor of COX-2), did not affect HO-1 expression. Pre-treating endothelial cells with AZD3582 at concns. that were effective at inducing HO-1 also reduced NADPH-dependent production of oxygen radicals. Antioxidant activity in the endothelial cells persisted after AZD3582 had been washed out from the incubation medium. When added exogenously to the cells at low micromolar concns., the HO-1 metabolite, bilirubin, virtually abolished NADPH-dependent oxidative stress. AZD3582-induced blockade of free-radical formation was reversed in the presence of the HO-1 inhibitor, tin protoporphyrin-IX (SnPP). Similar results were obtained in human gastric mucosal cells (KATO-III). Our results demonstrate that HO-1 is a novel target of AZD3582.
IT 163133-43-5, AZD3582
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AZD3582 increases heme oxygenase-1 expression and antioxidant activity in vascular endothelial and gastric mucosal cells)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

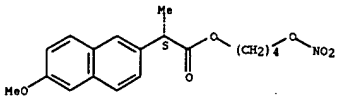


RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:414874 CAPLUS
DN 143:241563
TI Renal effects of the cyclooxygenase-inhibiting nitric oxide donator AZD3582 compared with rofecoxib and naproxen during normal and low sodium intake
AU Huledal, Gunilla; Jonzon, Bror; Malmenaes, Maria; Hedman, Ann; Andersson, Lars I.; Odlind, Bo; Brater, D. Craig
CS Experimental Medicine, Uppsala, SE-151, Swed.
SO Clinical Pharmacology & Therapeutics (New York, NY, United States) (2005), 77(5), 437-450
CODEN: CLPTAT; ISSN: 0009-9236
PB Elsevier
DT Journal
LA English
AB Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) and can thereby reduce renal function, especially with respect to solute excretion and renal perfusion. AZD3582 [4-(nitrooxy)butyl-(2S)-2-(6-methoxy-2-naphthyl)propanoate] is a COX-inhibiting nitric oxide donator. Donation of nitric oxide by AZD3582 could preserve blood flow and thereby counteract the deleterious effects of COX inhibition in the gastrointestinal tract and possibly in other organ systems, including the kidney. The aim of this single-dose study was to assess the hypothesis that AZD3582 would not adversely affect renal function compared with NSAIDs. Methods: In a parallel, randomized, double-blind fashion, a total of 60 healthy subjects (age range, 20-44 years) received 2 single doses of 750 mg AZD3582, 1500 mg AZD3582, 50 mg rofecoxib, 500 mg naproxen, or placebo (n = 12 per group). The first dose was given after a 5-day normal-sodium diet (150 mmol/d), and the second was given after a consecutive 3-day low-sodium diet (10 mmol/d). Urinary sodium excretion during normal sodium intake and glomerular filtration rate (GFR) (assessed by iohexol clearance) during sodium depletion were the primary variables measured. Results: Urinary sodium excretion was reduced in all active treatment groups (maximal reduction of approx. 11 mmol/h during normal sodium intake, P < .05 vs. placebo for all groups). GFR was also reduced in all active treatment groups. In sodium-depleted subjects, the mean (SD) maximal reduction in GFR during 0 to 6 h for 750 mg AZD3582, 1500 mg AZD3582, 50 mg rofecoxib, and 500 mg naproxen was 28.1 mL/min (13.5 mL/min), 33.7 mL/min (23.3 mL/min), 25.2 mL/min (29.2 mL/min), and 41.7 mL/min (30.7 mL/min), resp., with a statistically significant difference between 500 mg naproxen and placebo. Relative changes in sodium excretion and GFR were similar during normal sodium intake and sodium depletion during active treatment. Conclusion: The renal effects of 750 mg and 1500 mg AZD3582 were similar to those of 500 mg naproxen and 50 mg rofecoxib. Thus the potential for nitric oxide donation to create a renal-sparing agent was not found for AZD3582.
IT 163133-43-5, AZD3582
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-inhibiting nitric oxide donator AZD3582 was as effective as NSAIDs indicated by similar decrease in sodium excretion and GFR during normal sodium intake and sodium depletion by AZD3582, rofecoxib and naproxen in human)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

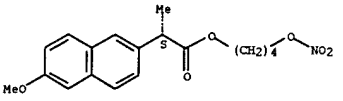
L14 ANSWER 11 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
(pre-clin. pharmacokinetics of the cyclooxygenase-inhibiting nitric oxide donor (CINOD) AZD3582)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



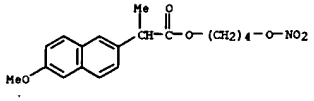
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:413958 CAPLUS
DN 143:70963
TI Pre-clinical pharmacokinetics of the cyclooxygenase-inhibiting nitric oxide donor (CINOD) AZD3582
AU Fagerholm, U.; Breuer, O.; Swedmark, S.; Hoogstraate, J.
CS Clinical Pharmacology, AstraZeneca R and D Soedertaelje, Soedertaelje, S-151 85, Swed.
SO Journal of Pharmacy and Pharmacology (2005), 57(5), 587-597
CODEN: JPPMAB; ISSN: 0022-3573
PB Pharmaceutical Press
DT Journal
LA English
AB The pre-clin. pharmacokinetics of AZD3582 (4-(nitrooxy)butyl-(2S)-2-(6-methoxy-2-naphthyl) propanoate) and its primary metabolites (naproxen and nitrate) were evaluated. AZD3582 had intermediate and passive intestinal permeability (40 times lower than for naproxen), high systemic plasma clearance (CL), substantial gastrointestinal hydrolysis, intermediate volume of distribution (Vss; ≥3.4 L kg-1) and half-life (t1/2; 7 h), negligible plasma protein binding (.apprx.0.1%), low/intermediate oral uptake (≥13% as intact substance) and low and varying oral bioavailability (mean 1.4% in minipigs and 3.9% in dogs). Following administration of therapeutically relevant oral doses, plasma concns. of AZD3582 were very low (≤ 13 nM in minipigs and ≤442 nM in dogs; rat data not available) and varying, and accumulation was not apparent. The pharmacokinetics of AZD3582 did not show apparent dose-, time- or gender-related dependency. In blood and intestine, AZD3582 was hydrolyzed to naproxen, nitrate and other metabolites. The rate of this conversion was higher in rats than in non-rodents, including man. Despite near-complete to complete uptake of the oral dose, AZD3582 administration resulted in a lower bioavailability (F) of total naproxen than naproxen administration: 55% and 85% relative bioavailability (Frel) in rats and minipigs, resp. An increased distribution to metabolizing tissues of naproxen (as AZD3582), and thereby enhanced naproxen CL, is believed to be responsible. Following dosing of AZD3582 or naproxen, the t1/2 of naproxen was 5, 9-10 and >40 h in rats, minipigs and dogs, resp. The Vss and CL for naproxen were small. Plasma protein binding was extensive, and saturation was observed within the therapeutic dose and concentration range. Intake of food prolonged the systemic absorption of naproxen in the minipig. The pharmacokinetics of naproxen did not show apparent time- or gender-related dependency. Following oral dosing of [3H]-, [14C]- and [15N]-AZD3582, most [14C]- and [3H]-activity was excreted in urine and expired air, resp. Seventeen per cent of [15N] was recovered in minipig urine as [15N]-nitrate. About 30% of [3H]-activity (naproxen and/or naproxen-related metabolites) was excreted in bile and re-absorbed. Concns. of [14C]-activity (nitrooxy-Bu group and/or its metabolites) in milk were higher than in plasma and [3H]-activity in milk. [3H]- and [14C]-excretion data indicated that intact AZD3582 was not excreted in urine, bile or milk to a significant extent. There was no apparent consistency between tissue distribution of [14C]- and [3H]-activity in the rat, which suggests rapid and extensive metabolism of extravascularly distributed AZD3582. A substantial increase of plasma nitrate levels was found after single and repeated oral doses of AZD3582 in the minipig. No inhibition or induction of CYP450 was found.
IT 163133-43-5, AZD3582
RL: PKT (Pharmacokinetics); BIOL (Biological study)

L14 ANSWER 13 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:300267 CAPLUS
DN 142:349032
TI Nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity
IN Bolla, Manlio; Santus, Giancarlo; De Soldato, Piero
PA Nicox S.A., Fr.
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005030224	A1	20050407	WO 2004-EP51551	20040720
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI EP 2003-292378	A	20030926		

OS MARPAT 142:349032
AB The invention discloses the use of nitrosylated analgesic and/or antiinflammatory drugs for the prevention and/or treatment of viral diseases and/or their complications.
IT 170591-17-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

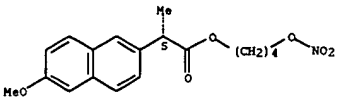


RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 14 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:250141 CAPLUS
DN 142:475921
TI A randomized, placebo controlled, comparative trial of the gastrointestinal safety and efficacy of AZD3582 versus naproxen in osteoarthritis
AU Lohmander, L. S.; McKeith, D.; Svensson, O.; Malmenas, M.; Bolin, L.; Kalla, A.; Genti, G.; Szechinski, J.; Ramos-Remus, C.; Catoggio, L.; Gutfraind, E.; Duhau, J.; Mysler, E.; Marcos, J.; Messina, O.; Cardoso Pucielli, M. L.; Batista de Miranda, J.; Barros Bertolo, M.; Goldenstein Schainberg, C.; Marques Neto, J. F.; Severino, N. R.; Gyulai, F.; Koo, E.; Szanyo, F.; Insperger, A.; Nafradi, L.; Balasz, T.; Buvar, A.; Molnar, A.; Gomori, E.; Nafradi, J.; Szekanecz, Z.; Tarjan, K.; Major, A.; Borbon, R.; Figueroa Gama, R. A.; Irazoque, F.; Jara, L. J.; Lino Perez, L.; Forthun, T.; Lonning, S. A.; Vassel, O.; Hoevik, H.; Mariadasan, K.; Vedvik, A.; Fonneloep, H.; Tandberg, A.; Hansen, Aa. N.; Tomala, T.; Jordet, B.; Bache, B. O.; Kubak, A.; Bo, O. E.; Stene, R.; Pedersen, T. M.; Andersen, M.; Nilsen, J. F.; Wall, A.; Lacki, J.; Mackiewicz, S.; Glowacka, M.; Kucharz, E.; Suchon, K.; Blacha, J.; Kwiatkowski, K.; Lipschitz, S.; Tikly, M.; van Duuren, E. M.; David, N.; Terblanche, J.; Lyddell, C.; Louw, I.; Mody, G.; Anderson, I.; Nell, H.; Middle, M. V.; McKinnon, C.; McGoldrick, H. P.; Salman, M.; Harding, C.; Taylor, S.; Robinson, J.; Maroni, J.; Fraser, J.; Sharma, S.; James, J.; Horne, C.; Anderson, M.; Norton, B.; Glekin, B.
CS Department of Orthopaedics, Medical Faculty, Lund University, Lund, Swed.
SO Annals of the Rheumatic Diseases (2005), 64(3), 449-456
CODEN: ARDIAO; ISSN: 0003-4967
PB BMJ Publishing Group
DT Journal
LA English
AB Objective: To evaluate the gastrointestinal safety and efficacy of the COX inhibiting nitric oxide donator AZD3582 in patients with hip or knee osteoarthritis. Methods: 970 patients were randomized (7:7:2) to AZD3582 750 mg twice daily, naproxen 500 mg twice daily, or placebo twice daily in a double blind study. The primary end point was the six week incidence of endoscopic gastroduodenal ulcers (diameter ≥3 mm). Overall damage measured on the Lanza scale was a secondary end point. Safety and tolerability assessments included endoscopic upper gastrointestinal erosions and the gastrointestinal symptom rating scale (GSRS). Efficacy was primarily assessed by WOMAC. Results: The incidence of ulcers with AZD3582 was 9.7% and with naproxen 13.7% (p=0.07, NS/, v 0% on placebo.). The incidence of Lanza scores >2 was higher with naproxen (43.7%) than with AZD3582 (32.2%) (p<0.001). Compared with baseline, significantly fewer ulcers and erosions developed in stomach and stomach/duodenum combined, and fewer erosions developed in stomach, duodenum, and both combined on AZD3582 than on naproxen. GSRS reflux and abdominal pain subscale scores were lower for AZD3582 than for naproxen but there was no difference for indigestion, constipation, and diarrhea. AZD3582 was as effective as naproxen at improving WOMAC scores. Both agents were well tolerated, with no significant effects on blood pressure. Conclusions: At doses with similar efficacy in relieving osteoarthritis symptoms, the primary end point of six week endoscopic gastroduodenal ulcer incidence was not significantly different between AZD3582 and naproxen. Most secondary endoscopic gastrointestinal end points favored AZD3582.
IT 163133-43-5, AZD3582
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

L14 ANSWER 14 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN . (Continued)
(AZD3582 similarly relieved osteoarthritic symptoms but assocd. with significantly lower incidence of endoscopic gastrointestinal ulcer than naproxen in patient with hip or knee osteoarthritis)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

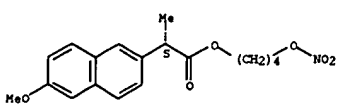
Absolute stereochemistry.



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:69896 CAPLUS
DN 142:309471
TI NSAIDs increase GM-CSF release by human synoviocytes: comparison with nitric oxide-donating derivatives
AU Zacharowski, Paula; Breese, Emma; Wood, Elizabeth; Del Soldato, Piero; Warner, Tim; Mitchell, Jane
CS Cardiac, Vascular and Inflammation Research, William Harvey Research Institute, Bart's and The London, Queen Mary School of Medicine and Dentistry, London, UK
SO European Journal of Pharmacology (2005), 508(1-3), 7-13
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier B.V.
DT Journal
LA English
AB Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat the condition of rheumatoid arthritis, where levels of prostaglandin E2 (PGE2) and granulocyte macrophage-colony stimulating factor (GM-CSF) are elevated in the synovial fluid. NO-NSAIDs are a new class of cyclooxygenase (COX)-inhibitors developed by coupling a nitric oxide (NO)-donating moiety to conventional NSAIDs. The authors show that, in cytokine-treated synoviocytes (from nonrheumatic patients), NO-naproxen and NO-flurbiprofen like their parent compds. concentration-dependently reduce the levels of PGE2 (an index of COX-2 activity), with a corresponding rise in the release of GM-CSF. Unlike acetylsalicylic acid (ASA), NO-ASA reduces the levels of PGE2, without increasing GM-CSF release, although cell viability is reduced at the highest concentration (1 mM). The effects of NSAIDs and NO-NSAIDs on GM-CSF release were attributable to the PGE2 mediated cAMP pathway because PGE2 reversed the effects of COX blockade. Second, phosphodiesterase inhibitors 3-isobutyl-1-methylxanthine (IBMX) and Ro-201724 (both of which elevate cAMP levels) decreased GM-CSF release, in the presence of PGE2. Finally, neither sodium nitroprusside nor zaprinast (both of which elevate cGMP levels) affected GM-CSF or PGE2 release. Our findings demonstrate that GM-CSF is regulated by NSAIDs and NO-NSAIDs via inhibition of COX and appears to be mediated via the cAMP pathway. NO-ASA is the exception, because it does not increase GM-CSF release, although at millimolar concns. cell viability is reduced.
IT 163133-43-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NSAIDs increase GM-CSF release by human synoviocytes and comparison with nitric oxide-donating derivs.)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

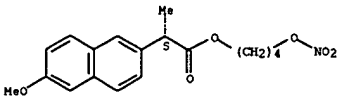


RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L14 ANSWER 16 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:1065694 CAPLUS
DN 142:68774
TI Nitric oxide (NO)-releasing naproxen (HCT-3012 [(S)-6-methoxy-α-methyl-2-naphthaleneacetic acid 4-(nitrooxy)butyl ester]) interactions with aspirin in gastric mucosa of arthritic rats reveal a role for aspirin-triggered lipoxin, prostaglandins, and NO in gastric protection
AU Fiorucci, Stefano; Di Lorenzo, Annarita; Renga, Barbara; Farneti, Silvana; Morelli, Antonio; Cirino, Giuseppe
CS Clinica di Gastroenterologia ed Epatologia, Dipartimento di Medicina Clinica e Sperimentale, Faculty of Medicine, Universita degli Studi di Perugia, Perugia, Italy
SO Journal of Pharmacology and Experimental Therapeutics (2004), 311(3), 1264-1271
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Administration of selective and nonselective cyclooxygenase (COX)-2 inhibitors to rheumatoid arthritis patients taking low doses of acetylsalicylic acid (ASA) for cardiovascular prevention assocs. with increased risk of gastrointestinal bleeding. The present study was undertaken to investigate whether administration of HCT-3012, a nitric oxide (NO)-releasing derivative of naproxen, exacerbates gastric mucosal injury in arthritic rats administered low doses of ASA. Our results demonstrated that while treating arthritic rats with a dose of 30 mg/kg/day ASA causes detectable mucosal injury, but had no effect on arthritis score and interleukin-6 plasma levels, coadministration of naproxen (10 mg/kg/day) and celecoxib (30 mg/kg/day), in combination with ASA from day 7 to day 21, attenuates arthritis development ($P < 0.01$ vs. arthritis alone), but markedly enhanced gastric mucosal damage caused by ASA ($P < 0.01$ vs. ASA alone). In contrast, coadministration of HCT-3012 (15 mg/kg/day) significantly attenuated arthritis development, because HCT-3012 was equally or more effective than naproxen and celecoxib in attenuating local and systemic inflammation ($P > 0.001$ vs. arthritis) without exacerbating gastric mucosal injury caused by ASA. Arthritis development assocs. with gastric COX-2 induction, mRNA and protein, and enhanced gastric prostaglandin E2 (PGE2) synthesis ($P < 0.01$ vs. control rats). Although all treatments, including celecoxib, were effective in reducing gastric PGE2 synthesis, administering arthritic rats with ASA resulted in a significant increase in gastric content of aspirin-triggered lipoxin (ATL), a COX-2-derived lipid mediator that regulates proinflammatory responses at the neutrophils/endothelial interface. Administering arthritic rats with naproxen and celecoxib abrogates ATL formation induced by ASA although enhanced neutrophils accumulate into the gastric mucosa ($P < 0.01$ vs. ASA alone). In contrast, whereas HCT-3012 inhibited ATL formation, it did not increase neutrophil recruitment into the gastric microcirculation. Collectively, these data indicate that NO derived from HCT-3012 has the potential to compensate for inhibition of PGE2 and ATL and to protect the gastric mucosa by limiting the recruitment of neutrophils. These data suggest that HCT-3012 might be a safer alternative to nonsteroidal anti-inflammatory drugs and coxibs in rheumatic patients that take low doses of ASA.
IT 163133-43-5, HCT-3012
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-releasing HCT-3012 interactions with aspirin in gastric mucosa of arthritic rats reveal a role for aspirin-triggered lipoxin, prostaglandins, and nitric oxide in gastric protection)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

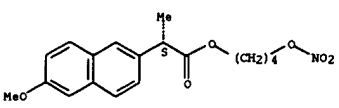
Absolute stereochemistry.



RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 17 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:608722 CAPLUS
DN 141:150761
TI The nitric oxide-releasing naproxen derivative displays cardioprotection in perfused rabbit heart submitted to ischemia-reperfusion
AU Rossoni, Giuseppe; Manfredi, Barbara; Del Soldato, Piero; Berti, Ferruccio
CS Departments of Pharmacological Sciences and Pharmacology, Chemotherapy, and Medical Toxicology, University of Milan, Milan, Italy
SO Journal of Pharmacology and Experimental Therapeutics (2004), 310(2), 555-562
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB In this study, the pharmacol. activity of HCT-3012 [(S)-6-methoxy-α-methyl-2-naphthaleneacetic acid 4-(nitrooxy)butyl ester], a nitric oxide (NO)-releasing derivative of naproxen, was compared with that of naproxen in a model of acute ischemia (40 min) and reperfusion (20 min) of the rabbit heart. HTC-3012 (3-100 μM), in spite of inhibition of 6-keto-prostaglandin F1α generation by the cardiac tissues, brought about a dose-dependent normalization of coronary perfusion pressure, associated with a reduction of ventricular contracture during ischemia with remarkable improvement of left ventricular developed pressure at reperfusion. These beneficial effects were accompanied by a substantial release of nitrite/nitrate in the heart perfusates, indicating that NO has been released by HCT-3012 and donated to the cardiac tissue. These events were paralleled by a significant reduction of creatine kinase activity in heart perfusates during reperfusion. Naproxen (10-100 μM) aggravated the myocardial damage in ischemic reperfused hearts, severely depressing the postischemic ventricular dysfunction. Perfusion of the heart with NG-monomethyl-l-arginine (10 μM) caused a marked aggravation of myocardial damage of the reperfused hearts, and this effect was dose dependently prevented by HCT-3012 but not by naproxen. The results of the present expts. clearly indicate that HCT-3012, by donating NO, displays a noticeable anti-ischemic effect in reperfused ischemic rabbit hearts. The safer gastrointestinal profile of HCT-3012 and its ability to control exptl. hypertension, suggest that this compound may have therapeutical potential in cardiovascular disease, namely in the prevention of myocardial ischemic events, and may represent a better alternative to conventional nonsteroidal anti-inflammatory drugs.
IT 163133-43-5, HCT 3012
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-releasing naproxen derivative displays cardioprotection in perfused rabbit heart submitted to ischemia-reperfusion)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

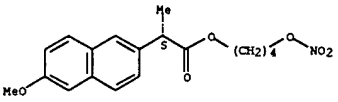
Absolute stereochemistry.



L14 ANSWER 17 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 18 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:579515 CAPLUS
DN 142:147485
TI New development of non-steroid anti-inflammatory drugs (NSAIDs)
AU Fu, De-cai; Wang, Shu-yue; Rong, Jie; Zhang, Shou-fang
CS College of Chemical and Pharmaceutical Engineering, Hebei University of Science and Technology, Shijiazhuang Hebei, 050018, Peop. Rep. China
SO Hebei Gongye Keji (2004), 21(3), 55-57
CODEN: HGKEFI; ISSN: 1008-1534
PB Hebei Gongye Keji Bianjibu
DT Journal; General Review
LA Chinese
AB A review. The development of new non-steroid anti-inflammatory drugs (NSAIDs) with high efficiency and minimal toxicity is based on the discovery of NO, which is an important message substance and has various physiol. effects. Compds. which combine traditional non-steroid anti-inflammatory drugs with NO-releasing substance would become new NSAIDs. The study has achieved a great development since 1990s.
IT 163133-43-5, HCT-3012
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new development of non-steroid anti-inflammatory drugs (NSAIDs))
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 19 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

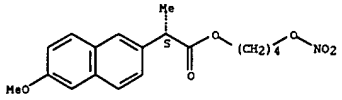
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 19 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:354783 CAPLUS
DN 140:350593
TI Use of NO-donating NSAIDs for the treatment of conditions associated with gastrointestinal motility
IN Jonzon, Bror; Hoogstraate, Janet
PA Astrazeneca UK Limited, UK
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004035042	A1	20040429	WO 2003-SE1603	20031015
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003269774	A1	20040504	AU 2003-269774	20031015
PRAI SE 2002-3093	A	20021018		
WO 2003-SE1603	W	20031015		

OS MARPAT 140:350593
AB The invention discloses the use of NO-donating nonsteroidal antiinflammatory drugs in the treatment of conditions associated with gastrointestinal motility, a method of treatment of such conditions, and the use of pharmaceutical compns. comprising one or more NO-donating NSAID(s) in the treatment of such conditions. More particularly, the invention is directed to the use of one or more NO-donating NSAID(s) for the manufacture of a medicament for the treatment of conditions associated with
disturbed gastrointestinal motility.
IT 163133-43-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO-donating NSAIDs for treatment of conditions associated with gastrointestinal motility)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



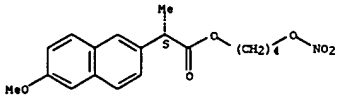
L14 ANSWER 20 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:203791 CAPLUS
DN 140:253349
TI Process for preparing nitrooxyalkyl esters of naproxen and bromonaproxen.
IN Del Soldato, Piero; Santus, Giancarlo; Benedini, Francesca
PA Nicox S.A., Fr.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004020384	A1	20040311	WO 2003-EP8698	20030806
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2497187	A1	20040311	CA 2003-2497187	20030806
AU 2003266966	A1	20040319	AU 2003-266966	20030806
EP 1532098	A1	20050525	EP 2003-747879	20030806
R: AT, BE, CH, DE, DX, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1678560	A	20051005	CN 2003-820605	20030806
JP 2005536558	T	20051202	JP 2004-532054	20030806
NZ 537993	A	20061130	NZ 2003-537993	20030806
ZA 2005000890	A	20060222	ZA 2005-890	20050131
US 2006173005	A1	20060803	US 2005-523722	20050914
PRAI IT 2002-MI1861	A	20020829		
WO 2003-EP8698	W	20030806		

OS CASREACT 140:253349; MARPAT 140:253349
AB RCO2(CR1R2)m(CR3R4)n(CR5R6)oXp(CR7R8)q(CR9R10)r(CR11R12)sONO2 [R = naproxen, bromonaproxen residue; R1-R12 = H, alkyl, aralkyl; m, n, o, q, r, s = 0-6; p = 0, 1; X = O, S, SO, SO2, NR13, PR13, (substituted) cycloalkylene, arylene, heterocyclylene; R13 = H, alkyl], were prepared by reaction of RCO2Z (R as defined above; Z = H, Li+, Na+, K+, Ca++, Mg++, tetralkylammonium, tetralkylphosphonium) with Y(CR1R2)m(CR3R4)n(CR5R6)oXp(CR7R8)q(CR9R10)r(CR11R12)sONO2 [Y = halo, BF4, SbF6, FSO3, ASO3; A = (substituted) alkyl; other variables as defined above]. Thus, a mixture of naproxen and KHCO3 was heated in DMF at 50-60° for 90 min.; the mixture was cooled to room temperature and treated with KI and 4-bromobutyl nitrate (preparation given) followed by stirring for
25 h to give 73% naproxen 4-nitrooxybutyl ester.
IT 163133-43-5P, (S)-2-(6-Methoxy-2-naphthyl)propanoic acid 4-nitrooxybutyl ester 669692-80-2P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

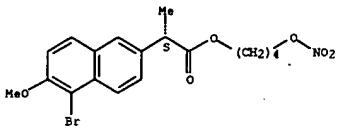
Absolute stereochemistry.

L14 ANSWER 20 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 669692-80-2 CAPLUS
CN 2-Naphthaleneacetic acid, 5-bromo-6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

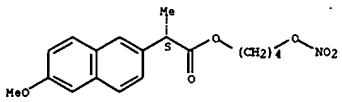
Absolute stereochemistry. Rotation (+).



RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 21 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:197525 CAPLUS
DN 141:235337
TI The CINOD, AZD3582, exhibits an improved gastrointestinal safety profile compared with naproxen in healthy volunteers
AU Jonzon, Bror; Bjarnason, Ingvar; Hawkey, Chris; Jones, John; Goddard, Andrew; Fagerholm, Urban; Karlsson, Paer
CS Experimental Medicine, AstraZeneca R and D Soedertaelje, Soedertaelje, S-151 85, Swed.
SO Inflammopharmacology (2003), 11(4-6), 437-444
CODEN: IAOAES; ISSN: 0925-4692
PB VSP BV
DT Journal; General Review
LA English
AB A review. COX-inhibiting nitric oxide donators (CINODs) are a new class of drugs in development for the treatment of acute and chronic pain. They comprise a COX-inhibiting moiety linked to a nitric-oxide-donating component and are designed to provide an innovative mechanism of action of balanced COX inhibition and controlled nitric oxide donation. Through these pathways, CINODs should provide analgesic and anti-inflammatory efficacy, while offering gastrointestinal safety through the tissue-protective effects of nitric oxide donation. AZD3582 [4-(nitrooxy)butyl-(2S)-2-(6-methoxy-2-naphthyl)propanoate] is the first agent in the CINOD class to enter extensive clin. development. Pre-clin. studies demonstrate that AZD3582 has a superior gastrointestinal safety profile to naproxen, while demonstrating analgesic and anti-inflammatory efficacy. In healthy human volunteers, AZD3582 caused little gastrointestinal damage compared with equimolar doses of naproxen. Studies to evaluate the longer-term gastrointestinal safety of AZD3582, alongside its efficacy in alleviating chronic and acute pain, are ongoing.
IT 163133-43-5, AZD3582
RL: ADV (Adverse effect, including toxicity); BMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CINOD AZD3582 was associated with little or no gastrointestinal damage, caused significantly fewer gastrointestinal erosions than naproxen in preclin. studies and caused little GI damage compared to naproxen in human)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

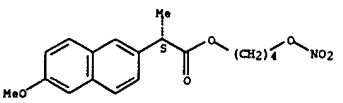
Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 22 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:197523 CAPLUS
DN 141:235335
TI COX-inhibiting nitric oxide donators (CINODs) - a new paradigm in the treatment of pain and inflammation
AU Hoogstraate, Janet; Andersson, Lars I.; Berge, Odd-Geir; Jonzon, Bror; Oejteg, Goeran
CS Research DMPK, AstraZeneca R and D Soedertaelje, Soedertaelje, S-151 85, Swed.
SO Inflammopharmacology (2003), 11(4-6), 423-428
CODEN: IAOAES; ISSN: 0925-4692
PB VSP BV
DT Journal; General Review
LA English
AB A review. The clin. utility of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief is tempered by their propensity to cause gastrointestinal toxicity. Cyclooxygenase (COX)-inhibiting nitric oxide donators (CINODs) are a new class of drugs designed to provide analgesic efficacy through COX inhibition and gastrointestinal safety through the protective effects of controlled nitric oxide donation. Pre-clin. studies assessing the pharmacol., efficacy and gastrointestinal safety of AZD3582 [4-(nitrooxy)butyl-(2S)-2-(6-methoxy-2-naphthyl)propanoate] support this concept. Based on these studies, AZD3582 was the first CINOD to enter clin. development for the treatment of acute and chronic pain. The potential clin. utility of this new class is illustrated by a study of AZD3582 in healthy volunteers in which it caused significantly less acute gastrointestinal toxicity than an equimolar dose of naproxen. The results of the animal studies and the initial clin. study warrant long-term tolerability studies of AZD3582 along with evaluation of its anti-inflammatory and analgesic effects in humans.
IT 163133-43-5, AZD3582
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CINOD AZD3528 produce COX inhibition, reduce gastrointestinal damage by local, systemic effect of nitric oxide donation in pain and inflammation, produce low toxicity in healthy human and needs clin. trial to determine tolerability)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

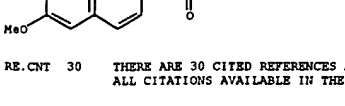
Absolute stereochemistry.



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 23 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:91194 CAPLUS
DN 141:17167
TI A common pathway of nitric oxide release from AZD3582 and glyceryl trinitrate
AU Berndt, Georg; Grosser, Nina; Hoogstraate, Janet; Schroder, Henning
CS School of Pharmacy, Department of Pharmacology and Toxicology, Martin Luther University, Halle (Saale), 06099, Germany
SO European Journal of Pharmaceutical Sciences (2004), 21(2-3), 331-335
CODEN: EPSCED; ISSN: 0928-0987
PB Elsevier B.V.
DT Journal
LA English
AB 4-(Nitrooxy)-butyl-(S)-2-(6-methoxy-2-naphthyl)-propanoate (AZD3582) is a cyclooxygenase (COX)-inhibiting nitric oxide donator (CINOD). It donates nitric oxide (NO) in biol. systems through as yet unidentified mechanisms; cGMP, a marker of intracellularly generated NO, was increased up to 27-fold over basal levels by AZD3582 (1-30 μM) in LLC-PK1 kidney epithelial cells. A 5 h pretreatment with glyceryl trinitrate (GTN, 0.1-1 μM) attenuated the cGMP response to a subsequent challenge with AZD3582 or GTN. Similarly, AZD3582 (10-30 μM) pretreatment reduced the increase in cGMP on subsequent incubation with AZD3582 or GTN. In contrast, cGMP stimulation by SIN-1, which releases NO independently of enzymic catalysis, remained unimpaired in cells pretreated with GTN or AZD3582. Our results demonstrate that AZD3582 decreases the sensitivity of the guanylyl cyclase/cGMP system to GTN and vice versa. This suggests that bioactivation pathways for organic nitrates, which involve enzymic catalysis, may be responsible for NO donation from AZD3582.
IT 163133-43-5
RL: BMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(a common pathway of nitric oxide release from AZD3582 and glyceryl trinitrate)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

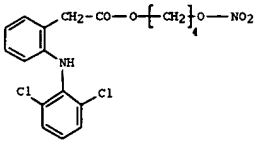


RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 24 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:2666 CAPLUS
DN 140:65191
TI Oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability
IN Del Soldato, Piero; Santus, Giancarlo; Macelloni, Cristina
PA Nicox S.A., Fr.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004000273	A1	20031231	WO 2003-EP6496	20030620
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2491152	A1	20031231	CA 2003-2491152	20030620
	AU 2003246564	A1	20040106	AU 2003-246564	20030620
	EP 1526839	A1	20050504	EP 2003-760660	20030620
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	CN 1665486	A	20050907	CN 2003-815181	20030620
	JP 2005530835	T	20051013	JP 2004-514802	20030620
	NZ 537204	A	20060728	NZ 2003-537204	20030620
	ZA 2004010109	A	20050902	ZA 2004-10109	20041214
	NO 2005000347	A	20050121	NO 2005-347	20050121
	US 2006171969	A1	20060803	US 2005-515621	20050912
PRAI	IT 2002-MI1392	A	20020625		
	WO 2003-EP6496	W	20030620		

GI

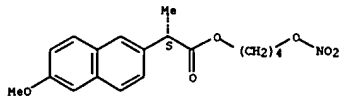


I

AB The present invention relates to new pharmaceutical compns. for the

L14 ANSWER 24 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
administration of liq. drugs in solid oral forms, said compns. comprising one or more active ingredients, one or more surface-active agents and optionally a co-surfactant and/or an absorption enhancer absorbed on a solid inert carrier. An emulsion was prepd. contg. I 100, Cremophor EL 50, Phospholipon 80H 50, Aerosil 200 100, and Explotab 100 g.
IT 163133-43-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

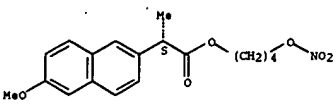
Absolute stereochemistry.



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 25 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:958703 CAPLUS
DN 140:297105
TI Gastrointestinal safety of AZD3582, a cyclooxygenase inhibiting nitric oxide donator: proof of concept study in humans
AU Hawkey, C. J.; Jones, J. I.; Atherton, C. T.; Skelly, M. M.; Bebb, J. R.; Fagerholm, U.; Jonzon, B.; Karlsson, P.; Bjarnason, I. T.
CS Division of Gastroenterology, University Hospital Nottingham, Nottingham, NG7 2UH, UK
SO Gut (2003), 52(11), 1537-1542
CODEN: GUTTAK; ISSN: 0017-5749
PB BMJ Publishing Group
DT Journal
LA English
AB Cyclooxygenase inhibiting nitric oxide donators (CINODs) are a new class of anti-inflammatory and analgesic drugs that may minimize gastrointestinal toxicity compared with standard non-steroidal anti-inflammatory drugs (NSAIDs) by virtue of nitric oxide donation. A proof of concept study of the gastrointestinal safety of AZD3582, the first CINOD available for human testing, was conducted. Thirty one subjects were randomized to receive placebo, naproxen 500 mg twice daily, or its nitroxybutyl derivative AZD3582 in an equimolar dose (750 mg twice daily) for 12 days in a double blind three period crossover volunteer study. At the start and end of each dosing period, gastroduodenal injury was assessed by endoscopy and small bowel permeability by differential urinary excretion of lactulose and L-rhamnose. Pharmacokinetic profiles were assessed at steady state. On naproxen, the mean total number of gastroduodenal erosions was 11.5 (and one subject developed an acute ulcer) vs. 4.1 on AZD3582 ($p<0.0001$). More than half of the subjects had no erosions on AZD3582. Differences were seen for both the stomach and duodenum. Naproxen increased intestinal permeability (lactulose:L-rhamnose ratio 0.030 before v 0.040 after treatment) whereas AZD3582 (0.029 before, 0.029 after; $p=0.006$ v naproxen) and placebo (0.030 before, 0.028 after; $p<0.001$ v naproxen) did not. The steady state bioavailability of naproxen metabolized from AZD3582 was 95% (95% confidence interval 87-101%) of that after naproxen administration. This human study supports animal data showing reduced gastrointestinal toxicity with the CINOD AZD3582. The potential combination of effective pain relief and gastrointestinal protection offered by AZD3582 warrants further evaluation in human clin. studies.
IT 163133-43-5, AZD 3582
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gastrointestinal safety of AZD3582, cyclooxygenase inhibiting nitric oxide donator)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



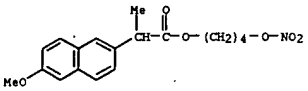
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD

L14 ANSWER 25 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 26 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:818296 CAPLUS
DN 139:302040
TI Nitrooxy derivatives of antiinflammatory/analgesic compounds for the treatment of arthritis
IN Del Soldato, Piero
PA Nicox S.A., Fr.
SO PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003084550	A1	20031016	WO 2003-EP3183	20030327
	W: AE, AG, AL, AU, BA, BB, BR, BZ, CA, CN, CO, CR, CU, DM, DZ, EC, GD, GE, HR, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, SG, TN, TT, UA, US, UZ, VN, YU, ZA				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	IT 2002MI0773	A1	20031013	IT 2002-MI773	20020411
	AU 2003224002	A1	20031020	AU 2003-224002	20030327
	EP 1492543	A1	20050105	EP 2003-720377	20030327
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2005522472	T	20050728	JP 2003-581790	20030327
PRAI	IT 2002-MI773	A	20020411		
	WO 2003-EP3183	W	20030327		

OS MARPAT 139:302040
AB Antiinflammatory and/or antiinflammatory/analgesic compds. having the formula A(B)b0(C)c0-N(O)s [A contains radical of nonsteroidal antiinflammatory or nonsteroidal antiinflammatory/analgesic drug; B, C = bivalent linking group; s = 1, 2; b0, c0 = 0, 1 (with proviso)], and salts thereof, are disclosed for use in the treatment of arthritis.
IT 170591-17-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment of arthritis)
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 26 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

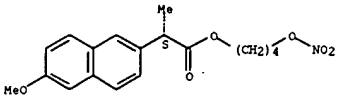
L14 ANSWER 27 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:777566 CAPLUS
DN 139:281272
TI Nitric oxide-donating NSAIDS adsorbed into carrier particles
IN Morein, Sven; Berg, Mats; Holmberg, Christina; Lundberg, Per Johan; Anders, Ringberg
PA Astrazeneca Ab, Swed.; Astrazeneca Uk Limited
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003080029	A1	20031002	WO 2003-SE468	20030320
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003216006	A1	20031008	AU 2003-216006	20030320
	EP 1490033	A1	20041229	EP 2003-745055	20030320
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	US 2005129774	A1	20050616	US 2003-507368	20030320
	JP 2005533751	T	20051110	JP 2003-577859	20030320
PRAI	SE 2002-895	A	20020322		
	WO 2003-SE468	W	20030320		

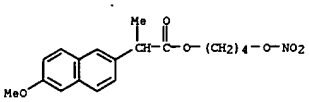
AB The present invention relates to porous particles comprising NO-donating nonsteroidal anti-inflammatory compound optionally mixed with surfactants and to new solid drug delivery composition comprising the particles optionally in combination with a second active drug. Furthermore, the invention relates to processes for producing the porous particles and solid drug delivery composition as well as the use of the composition in the manufacture of a medicament. The NO-donating NSAID may be in an oily or melted form. Thus, a tablet comprised 4-(nitrooxy)butyl (S)-2-(9-methoxy-2-naphthyl)propanoate (I) 250 and omeprazole 20 mg. Enteric over-coated pellets comprised omeprazole and a powder of the porous particles containing I were manufactured sep. before compressing the 2 components.
IT 163133-43-5 170591-17-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-donating NSAIDS adsorbed into carrier particles)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L14 ANSWER 27 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



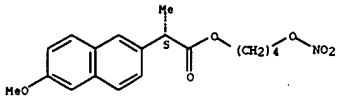
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 28 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:604857 CAPLUS
DN 139:223534
TI NO-naproxen AstraZeneca
AU Monck, Nat
CS Vernalis Research Ltd, Wokingham, RG41 5UA, UK
SO IDrugs (2003), 6(6), 593-599
CODEN: IDRUFN; ISSN: 1369-7056
PB Current Drugs
DT Journal; General Review
LA English
AB A review. NO-naproxen, consisting of the NSAID naproxen linked to a nitric oxide (NO) moiety, is under development by AstraZeneca plc, under license from NicOx SA, for the potential treatment of acute/chronic pain.
IT 163133-43-5, Nitronaproxen
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of NO-naproxen (nitronaproxen) for the potential treatment of acute and chronic pain)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

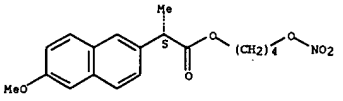
L14 ANSWER 29 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:434515 CAPLUS
DN 139:22023
TI Preparation of (S)-naproxen 4-nitrooxybutyl ester for treatment of pain
IN Belli, Aldo; Cannata, Vincenzo; Fonduca, Telly; Hedberg, Martin; Westermark, Andreas; Villa, Marco
PA Astrazeneca A.B., Swed.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003045896	A1	20030605	WO 2002-SE2184	20021126
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2465697	A1	20030605	CA 2002-2465697	20021126
	AU 2002365372	A1	20030610	AU 2002-365372	20021126
	EP 1451140	A1	20040901	EP 2002-791150	20021126
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2005510557	T	20050421	JP 2003-547348	20021126
	US 2005234123	A1	20051020	US 2005-497012	20050609
PRAI	SE 2001-3978	A	20011127		
	WO 2002-SE2184	W	20021126		

OS CASREACT 139:22023; MARPAT 139:22023
AB The present invention relates to a new process for the preparation of the (S)-naproxen 4-nitrooxybutyl ester and to new intermediates obtained and used therein. The invention further relates to the use of the new intermediates for the manufacturing of pharmaceutically active compds. such as (S)-naproxen 4-nitrooxybutyl ester. The invention also relates to the use of (S)-naproxen 4-nitrooxybutyl ester prepared according to the process of the present invention for the manufacturing of a medicament for the treatment of pain.
IT 163133-43-5P
RL: IMF (Industrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (S)-naproxen 4-nitrooxybutyl ester for treatment of pain)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L14 ANSWER 29 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



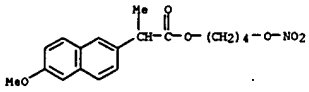
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 30 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:221490 CAPLUS
DN 138:260440
TI Self emulsifying drug delivery system containing NSAIDs
IN Holmberg, Christina
PA Astrazeneca AB, Swed.
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003022249	A1	20030320	WO 2002-SE1598	20020905
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1427392	A1	20040616	EP 2002-765747	20020905
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2005504788	T	20050217	JP 2003-526379	20020905
	US 2004248974	A1	20041209	US 2004-488585	20040304
PRAI	SE 2001-2993	A	20010907		
	WO 2002-SE1598	W	20020905		

OS MARPAT 138:260440
AB A pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprises 1 or more NO-releasing NSAID(s), 1 or more surfactants, of which at least one is phospholipid, the composition forming an in-situ oil-in-water emulsion upon contact with gastrointestinal fluids. The composition may optionally also comprise an addnl. oil or semi-solid fat. Further, 1 or more short-chain alcs. can optionally be included in the composition Also within the scope of the invention is a combination with a proton pump inhibitor. The pharmaceutical composition is useful in the treatment of pain and inflammation. Further within the scope of the invention is kit comprising a pharmaceutical composition according to the invention in a unit dosage form, in combination with a proton pump inhibitor, and the proton pump inhibitor is enteric coated. Thus, a formulation contained Lipoid S100 0.30, propylene glycol 0.90, and a NO-releasing NSAID 4.00 g.
IT 170591-17-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system containing NSAIDs)
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

L14 ANSWER 30 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



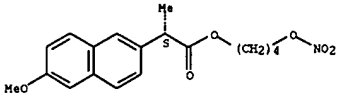
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 31 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:133017 CAPLUS
DN 138:163547
TI Nitrooxy compounds for treatment of vasculopaties
IN Del Soldato, Piero
PA Nicox S.A., Fr.
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003013499	A2	20030220	WO 2002-EP8374	20020726
	WO 2003013499	A3	20031231		
	W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TN, TR, TT, UA, US, UZ, VN, YU, ZA				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	IT 2001MI1744	A1	20030210	IT 2001-MI1744	20010809
	AU 2002333276	A1	20030224	AU 2002-333276	20020726
PRAI	IT 2001-MI1744	A	20010809		
	WO 2002-EP8374	W	20020726		

OS MARPAT 138:163547
AB The invention discloses the use for vasculopathy treatment of nitrooxy compds. (Markush included), or salts thereof. Compds. of the invention include e.g. 2-fluoro-α-methyl-4-diphenylacetic acid (4-nitrooxy)butyl ester (NO-flurbiprofen).
IT 163133-43-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrooxy compds. for treatment of vasculopaties)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

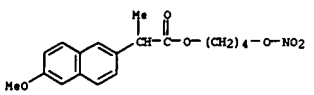
Absolute stereochemistry.



L14 ANSWER 32 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:736089 CAPLUS
DN 137:253012
TI Pharmaceutical compositions containing NO-releasing NSAID and surfactants
IN Siekmann, Britta; Thoring, Barbro
PA Astrazeneca AB, Swed.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002074282	A1	20020926	WO 2002-SE476	20020313
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2435825	A1	20020926	CA 2002-2435825	20020313
	EP 1370239	A1	20031217	EP 2002-704035	20020313
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	CN 1496253	A	20040512	CN 2002-806527	20020313
	BR 2002007760	A	20040601	BR 2002-7760	20020313
	JP 2004523577	T	20040805	JP 2002-572990	20020313
	ZA 2003006282	A	20041123	ZA 2003-6282	20030813
	US 2004096494	A1	20040520	US 2003-471378	20030909
	NO 2003004026	A	20031111	NO 2003-4026	20030911
PRAI	SE 2001-901	A	20010315		
	WO 2002-SE476	W	20020313		

OS MARPAT 137:253012
AB A new pharmaceutical composition in the form of lipoglobules comprises (a) 1 or more NO-releasing NSAIDs; (b) 1 or more surfactants; and (c) an aqueous phase, and is useful for the treatment of pain and inflammation. Thus, a composition contained 4-(nitrooxy)butyl 6-methoxy-α-methyl-2-naphthaleneacetate 0.77, fractionated coconut oil 2.97, Phospholipon-80 0.76, and Poloxamer-407 1.61 mg/g.
IT 170591-17-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing NO-releasing NSAID and surfactants)
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



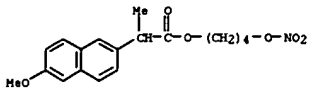
L14 ANSWER 32 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 33 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:676579 CAPLUS
DN 135:231708
TI New self emulsifying drug delivery system
IN Holmberg, Christina; Siekmann, Britta
PA AstraZeneca AB, Swed.
SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001066088	A1	20010913	WO 2001-SE467	20010306
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2401498	A1	20010913	CA 2001-2401498	20010306
	EP 1267832	A1	20030102	EP 2001-910305	20010306
	EP 1267832	B1	20040602		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001009014	A	20030603	BR 2001-9014	20010306
	JP 2003525894	T	20030902	JP 2001-564741	20010306
	HU 200300882	A2	20030929	HU 2003-882	20010306
	EE 200200500	A	20040216	EE 2002-500	20010306
	AT 268162	T	20040615	AT 2001-910305	20010306
	NZ 521009	A	20040625	NZ 2001-521009	20010306
	PT 1267832	T	20040930	PT 2001-910305	20010306
	ES 2220728	T3	20041216	ES 2001-1910305	20010306
	RU 2270675	C2	20060227	RU 2002-122744	20010306
	ZA 2002006740	A	20031124	ZA 2002-6740	20020822
	US 2003161846	A1	20030828	US 2002-220791	20020905
	NO 2002004272	A	20021105	NO 2002-4272	20020906
	HK 1050632	A1	20050318	HK 2003-102781	20030416
PRAI	SE 2000-773	A	20000308		
	WO 2001-SE467	W	20010306		

OS MARPAT 135:231708
AB The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising: 1 or more NO-releasing NSAID(s), 1 or more surfactants, optionally an addnl. oil or semi-solid fat. The composition forms an in-situ oil-in-water emulsion upon contact with gastrointestinal fluids. The composition may optionally also comprise 1 or more short-chain alcs. Also within the scope of the invention is a combination with a proton pump inhibitor. The pharmaceutical composition is useful in the treatment of pain and inflammation. Further within the scope of the invention is kit comprising a pharmaceutical composition according to the invention in a unit dosage form, in combination with a proton pump inhibitor, and the proton

L14 ANSWER 33 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
pump inhibitor is enteric coated. Thus, a semisolid formulation contained a NO-releasing NSAID 750, Pluronic F127 450, and omeprazole 20 g.
IT 170591-17-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system)
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



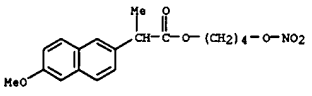
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 34 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:676578 CAPLUS
DN 135:231707
TI New self emulsifying drug delivery system
IN Holmberg, Christina; Siekmann, Britta
PA AstraZeneca AB, Swed.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001066087	A1	20010913	WO 2001-SE466	20010306
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2401857	A1	20010913	CA 2001-2401857	20010306
	EP 1267831	A1	20030102	EP 2001-910304	20010306
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001009012	A	20030603	BR 2001-9012	20010306
	HU 200300539	A2	20030728	HU 2003-539	20010306
	JP 2003525893	T	20030902	JP 2001-564740	20010306
	EE 200200483	A	20040216	EE 2002-483	20010306
	AT 311173	T	20051215	AT 2001-910304	20010306
	RU 2275908	C2	20060510	RU 2002-122745	20010306
	ES 2253354	T3	20060601	ES 2001-1910304	20010306
	NO 2002004194	A	20020903	NO 2002-4194	20020903
	ZA 2002007109	A	20031204	ZA 2002-7109	20020904
	US 2003077303	A1	20030424	US 2002-221079	20020905
PRAI	SE 2000-774	A	20000308		
	WO 2001-SE466	W	20010306		

AB The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising a nitro-group-containing naproxen ester (I) , 1 or more surfactants, an oil or a semi-solid fat; the composition forming an in-situ oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids. The composition may optionally also comprise 1 or more short-chain alcs. The pharmaceutical composition is useful in the treatment of pain and inflammation. Thus, a semisolid formulation contained I 3, Pluronic L 127 0.843, sorbitan monolaurate 0.282, and propylene glycol 0.375 g.
IT 170591-17-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system)
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)

L14 ANSWER 34 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 35 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:115100 CAPLUS
DN 134:178355
TI Process for the preparation of naproxene nitroxyalkyl esters
IN Benedini, Francesca; Oldani, Erminio; Castaldi, Graziano; Tarquini, Antonio
PA Nicox S.A., Fr.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001010814	A1	20010215	WO 2000-EP7222	20000727
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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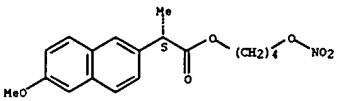
	EP 1200386	A1	20020502	EP 2000-951456	20000727
	EP 1200386	B1	20031001		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	TR 200200290	T2	20020521	TR 2002-290	20000727
	BR 2000012915	A	20020604	BR 2000-12915	20000727
	HU 200202435	A2	20021128	HU 2002-2435	20000727
	JP 2003506425	T	20030218	JP 2001-515282	20000727
	AT 251109	T	20031015	AT 2000-951456	20000727
	EP 1384707	A1	20040128	EP 2003-102132	20000727
	EP 1384707	B1	20050608		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, FI, CY				
	PT 1200386	T	20040227	PT 2000-951456	20000727
	ES 2208390	T3	20040616	ES 2000-951456	20000727
	AU 778694	B2	20041216	AU 2000-64385	20000727
	RU 2248348	C2	20050320	RU 2002-102860	20000727
	AT 297372	T	20050615	AT 2003-102132	20000727
	ES 2243859	T3	20051201	ES 2003-3102132	20000727
	ZA 2002000478	A	20030818	ZA 2002-478	20020118
	US 6700011	B1	20040302	US 2002-31412	20020118
	NO 2002000515	A	20020201	NO 2002-515	20020201
	ZA 2003004525	A	20040211	ZA 2003-4525	20030610
	US 2005119339	A1	20050602	US 2003-625558	20030724
PRAI	IT 1999-MI1753	A	19990804		
	EP 2000-951456	A3	20000727		
	WO 2000-EP7222	W	20000727		
	US 2002-31412	A3	20020118		

OS CASREACT 134:178355; MARPAT 134:178355
AB A process for obtaining nitroxyalkyl esters of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, was characterized in that a halide of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert organic

L14 ANSWER 35 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
solvent with an aliph. nitroxyalkanol HO-Y-ONO2, wherein Y is a C2-C20 alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as defined contg. a cycloalkylene as defined, in the presence of an inorg. base. E.g., to a soln. of 4-nitroxybutan-1-ol and K2CO3 in dichloromethane is added 2-(S)-(6-methoxy-2-naphthyl)propanoic acid chloride, to give the 4-nitroxybutyl ester of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (85%, ee 98%).
IT 163133-43-5P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of naproxene nitroxyalkyl esters)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

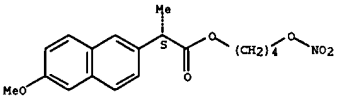


RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 36 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:1455 CAPLUS
DN 135:70874
TI Gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs
AU Brzozowski, T.; Konturek, P. Ch.; Konturek, S. J.; Sliwowski, Z.; Drozdowicz, D.; Kwiecien, S.; Pajdo, R.; Ptak, A.; Pawlik, M.; Hahn, E.
CS Department of Physiology, Jagiellonian University School of Medicine, Krakow, 31-531, Pol.
SO Digestive and Liver Disease (2000), 32(7), 583-594
CODEN: DLDIFK
PB Pacini Editore
DT Journal
LA English
AB Background & Aim. New class of nitric oxide-releasing non-steroidal anti-inflammatory drugs was shown to inhibit cyclooxygenase and prostaglandin generation without causing mucosal damage but whether these agents are capable of affecting gastric mucosal damage induced by strong irritants and healing of chronic gastric ulcers remains to be studied. In this investigation, effects of nitric oxide-releasing aspirin and nitric oxide-releasing naproxen were compared with those of native agents on gastric lesions provoked by 100% ethanol and on healing of chronic acetic acid ulcers. Results. Both, nitric oxide-releasing aspirin and naproxen dose-dependently attenuated ethanol-induced damage and produced a significant rise in gastric blood flow but did not delay healing of gastric ulcers while native aspirin and naproxen had no influence on ethanol-induced gastric damage but significantly prolonged ulcer healing, reduced gastric blood flow and suppressed mucosal generation of prostaglandin E2. The gastroprotective and hyperemic effects of both nitric oxide-non-steroidal anti-inflammatory drugs were completely abolished by ODQ, an inhibitor of guanylyl cyclase-cGMP system but not influenced by suppression of nitric oxide-synthase with L-NNA. The damaging effects of native acetyl salicylate acid or naproxen were aggravated by acidification of these non-steroidal anti-inflammatory drugs but the exogenous acid added to nitric oxide-acetyl salicylate acid or nitric oxide-naproxen failed to influence their effect. Despite inhibiting of PGE2 generation, both nitric oxide-releasing derivs. and native aspirin and naproxen failed to affect expression of cyclooxygenase-1 mRNA but upregulated the cyclooxygenase-2 mRNA. Concurrent inhibition of cyclooxygenase-2 by selective inhibitor NS-398 which by itself delayed ulcer healing and attenuated the gastric blood flow at ulcer margin, significantly worsened the effects of these nitric oxide-non-steroidal anti-inflammatory drugs and their parent drugs on ulcer healing and the gastric blood flow at the ulcer margin. Conclusions. Coupling of nitric oxide to aspirin or naproxen attenuates ethanol-induced damage, possibly due to an increase in gastric microcirculation mediated by excessive release and action of nitric oxide that probably compensates for PG deficiency induced by non-steroidal anti-inflammatory drugs; and nitric oxide-non-steroidal anti-inflammatory drug, unlike classic non-steroidal anti-inflammatory drugs, does not affect intact gastric mucosa and fails to delay the healing of pre-existing ulcers.
IT 163133-43-5, HCT 3012
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

L14 ANSWER 36 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

Absolute stereochemistry.



RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 37 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2000:861483 CAPLUS
DN 134:25340
TI New use of compounds as antibacterial agents
IN Eek, Arne; Raud, Johan
PA Astrazeneca AB, Swed.
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000072838	A1	20001207	WO 2000-SE1071	20000525
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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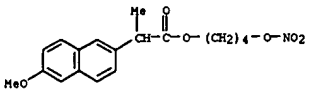
	TW 243672	B	20051121	TW 2000-89109689	20000519
	CA 2373653	A1	20001207	CA 2000-2373653	20000525
	BR 2000011116	A	20020219	BR 2000-11116	20000525
	EP 1196155	A1	20020417	EP 2000-937451	20000525
	EP 1196155	B1	20040804		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	TR 200103474	T2	20020422	TR 2001-3474	20000525
	HU 200201502	A2	20020828	HU 2002-1502	20000525
	JP 2003500442	T	20030107	JP 2000-620950	20000525
	EE 200100647	A	20030217	EE 2001-647	20000525
	NZ 515317	A	20040528	NZ 2000-515317	20000525
	AT 272396	T	20040815	AT 2000-937451	20000525
	AU 780678	B2	20050407	AU 2000-52623	20000525
	RU 2252032	C2	20050520	RU 2001-135826	20000525
	US 6593339	B1	20030715	US 2000-673007	20000929
	ZA 2001009497	A	20030217	ZA 2001-9497	20011116
	BG 106158	A	20020628	BG 2001-106158	20011128
	NO 2001005855	A	20020130	NO 2001-5855	20011130
	HK 1045814	A1	20050401	HK 2002-107373	20021009
	US 2004048917	A1	20040311	US 2003-426952	20030501
PRAI	SE 1999-2027	A	19990601		
	SE 1999-4704	A	19991221		
	WO 2000-SE1071	W	20000525		
	US 2000-673007	A1	20000929		

AB The present invention discloses a new use of NO-releasing NSAIDs, especially NO-releasing NSAIDs of formula (I), or a pharmaceutically acceptable salt or enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections, especially caused or mediated by Helicobacter pylori. Disclosed is also the new use of a NO-releasing NSAID in combination with an acid susceptible proton pump inhibitor for the treatment of bacterial infections.
IT 170591-17-0

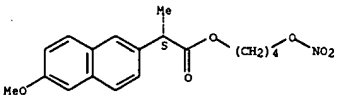
L14 ANSWER 37 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of Helicobacter pylori infections with nitric oxide-releasing NSAIDs and proton pump inhibitors)
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 38 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2000:557438 CAPLUS
DN 133:232547
TI NO-naproxen modulates inflammation, nociception and downregulates T cell response in rat Freund's adjuvant arthritis
AU Cicala, Carla; Ianaro, Angela; Fiorucci, Stefano; Calignano, Antonio; Bucci, Mariarosaria; Gerli, Roberto; Santucci, Luca; Wallace, John L.; Cirino, Giuseppe
CS Dipartimento di Farmacologia Sperimentale, Universita degli Studi di Napoli - Federico II, Naples, 80131, Italy
SO British Journal of Pharmacology (2000), 130(6), 1399-1405
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB Anti-inflammatory non steroidal drugs releasing NO (NO-NSAIDs) are a new class of anti-inflammatory drugs to which has been added an NO-releasing moiety. These compds. have been shown to retain the anti-inflammatory, analgesic and antipyretic activity of the parent compound but to be devoid of gastrointestinal (GI) toxicity. Freund's adjuvant (FA) arthritis was induced in rats by a single intraplantar injection into the right hindpaw of 100 μl of mycobacterium butyricum (6 mg ml-1). The effect of equimolar doses of naproxen (1, 3 and 10 mg kg-1) and NO-naproxen (1.5, 4.5 and 16 mg kg-1) was evaluated using two dosage regimen protocols: (i) preventive, starting oral administration of the drugs at the time of induction of arthritis and for the following 21 days (day 1-21); (ii) therapeutic, starting oral administration of the drugs 7 days after adjuvant injection and for the following 14 days (day 7-21). Hindpaw swelling (days 3, 7, 11, 14, 17, 21) and nociception (days 15 and 21) were measured. On day 22 rats were sacrificed, draining lymph nodes were removed and T cells isolated. In vitro proliferation of T cells following stimulation with Con A (0.5-5 μg ml-1) was measured using a tritiated thymidine incorporation assay. IL-2 receptor expression on T cells was measured by FACS anal. Naproxen and NO-naproxen showed similar activity in reducing edema formation in the non-injected (controlateral) hindpaw. Both drugs showed anti-nociceptive effect. NO-naproxen was anti-nociceptive at a dose of 4.5 mg kg-1 while naproxen showed the same extent of inhibition only at a dose of 10 mg kg-1. T cells were isolated and characterized by FACS anal. Stimulation of isolated T cells with concanavallin A in vitro caused a significant increase in thymidine uptake. NO-naproxen at a dose of 4.5 mg kg-1 inhibited T cell proliferation to the same extent as 10 mg kg-1 of naproxen. Inhibition of T cell proliferation was well correlated with reduced IL-2 receptor expression on T cells. In addition, NO-naproxen reduced both IL-1β and TNFα plasma levels while naproxen reduced IL-1β levels only. In conclusion, both naproxen and NO-naproxen reduce inflammation and nociception associated with arthritis. In addition NO-naproxen interferes to a larger extent with cellular mechanism involved in T cell activation in rat adjuvant arthritis indicating that introduction of the NO moiety in the naproxen structure increases the effect at the level of the immune system.
IT 163133-43-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO-naproxen modulates inflammation, nociception and downregulates T cell response in arthritis)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

L14 ANSWER 38 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
Absolute stereochemistry.

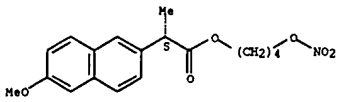


RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 39 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1999:257300 CAPLUS
DN 131:97177
TI Nitric oxide-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα
AU Fiorucci, S.; Santucci, L.; Federici, B.; Antonelli, E.; Distrutti, E.; Morelli, O.; Renzo, G. Di; Costa, G.; Cirino, G.; Soldato, P. Del; Morelli, A.
CS Clinica di Gastroenterologia ed Epatologia, Policlinico Monteluce, Perugia, 06100, Italy
SO Alimentary Pharmacology and Therapeutics (1999), 13(3), 421-435
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB Background: Nitric oxide (NO)-releasing NSAIDs are a new class of NSAID derivs. with markedly reduced gastrointestinal toxicity. Although it has been demonstrated that NO-NSAIDs spare gastric mucosal blood flow, mol. determinants involved in this effect are unknown. Aim: To investigate the effect of aspirin, naproxen and flurbiprofen, and their NO-derivs., on gastric apoptosis and endothelial cell damage induced by tumor necrosis factor-α (TNFα). In other systems, TNFα-induced apoptosis is mediated by caspases, a growing family of cysteine proteases similar to the IL-1β converting enzyme (ICE), and so we have investigated whether NO-NSAIDs modulate ICE-like endopeptidases. Methods: Rats were treated orally with aspirin, naproxen and flurbiprofen, or their NO-releasing derivs. in equimolar doses, and were killed 3 h later to assess mucosal damage and caspase activity. Endothelial cells (HUVECs) were obtained from human umbilical cord by enzymic digestion. Caspase 1 and 3 activities were measured by a fluorimetric assay using selective peptides as substrates and inhibitors. Apoptosis was quantified by ELISA specific for histone-associated DNA fragments and by the terminal transferase nick-end translation method (TUNEL). Results: In vivo NSAID administration caused a time-dependent increase in gastric mucosal damage and caspase activity. NCX-4016, NO-naproxen and NO-flurbiprofen did not cause any mucosal damage and prevented cysteine protease activation. NSAIDs and NO-NSAIDs stimulated TNFα release. Exposure to TNFα resulted in a time- and concentration-dependent HUVEC apoptosis, an effect that was prevented by pretreating the cells with NCX-4016, NO-naproxen, NO-flurbiprofen, SNP or Z-VAD.FMK, a pan-caspase inhibitor. The activation of ICE-like cysteine proteases was required to mediate TNFα-induced apoptosis of HUVECs. Exogenous NO donors inhibited TNFα-induced cysteine protease activation. Inhibition of caspase activity was due to S-nitrosylation of ICE/CPP32-like proteases. NO-NSAIDs prevented IL-1β release from endotoxin-stimulated macrophages. Conclusions: NO-releasing NSAIDs are a new class of non-peptide caspase inhibitors. Inhibition of ICE-like cysteine proteases prevents endothelial cell damage induced by pro-inflammatory agents and might contribute to the gastro-protective effects of NO-NSAIDs.
IT 163133-43-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced

L14 ANSWER 39 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
by TNFα)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

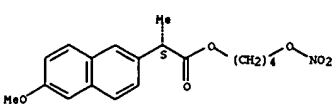
Absolute stereochemistry.



RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 40 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1998:181750 CAPLUS
DN 128:303783
TI Effect of a nitric oxide-releasing naproxen derivative on hypertension and gastric damage induced by chronic nitric oxide inhibition in the rat
AU Muscara, Marcelo N.; McKnight, Webb; Del Soldato, Piero; Wallance, John L.
CS Dep. Pharmacology and Therapeutics, Univ. Calgary, Calgary, AB, Can.
SO Life Sciences (1998), 62(15), PL235-PL240
CODEN: LIFSAK; ISSN: 0024-3205
PB Elsevier Science Inc.
DT Journal
LA English
AB NSAIDs can elevate blood pressure through mechanisms such as renal vasoconstriction and sodium retention. These effects are particularly evident in hypertensive individuals. Nitric oxide-releasing NSAID derivs. have been shown to have greatly reduced toxicity in the gastrointestinal tract and kidney. We therefore evaluated the effects of a 4 wk treatment with either naproxen or its nitric oxide-releasing derivative (NO-naproxen) on systemic arterial blood pressure and gastric damage in rats in which hypertension was induced by L-NAME. Rats received either L-NAME dissolved in the drinking water (400 mg/L) or tap water (control). Vehicle, naproxen (10 mg/kg) or an equimolar dose of NO-naproxen (14.5 mg/kg) were administered orally each day. After 4 wk, blood pressure was measured, blood samples were taken for measurement of thromboxane synthesis, and gastric damage was evaluated by blind, macroscopic scoring. Both naproxen and NO-naproxen inhibited systemic cyclooxygenase activity by >90%. NO-naproxen-treated rats exhibited no significant gastric damage. The gastric damage produced by L-NAME alone was potentiated by naproxen but prevented by NO-naproxen. L-NAME treatment significantly increased blood pressure. In the absence of L-NAME, the naproxen group had significantly higher blood pressure than both the control and NO-naproxen groups. IN rats receiving L-NAME, the same conclusions apply, but the concomitant administration of NO-naproxen was able to significantly reduce the blood pressure compared to L-NAME alone. Based on these results, we conclude that NO-naproxen may represent a safer alternative to standard NSAIDs in the treatment of inflammatory conditions in hypertensive patients.
IT 163133-43-5
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adverse effects of NSAID NO-naproxen as antiinflammatory agent for hypertensive patients)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 40 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L14 ANSWER 41 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1997:594647 CAPLUS
DN 127:257627
TI Nitric oxide donors capable of reducing renal, gastrointestinal, or respiratory drug toxicity
IN Del Soldato, Piero
PA Nicox S.A., Fr.; Del Soldato, Piero
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9731654	A1	19970904	WO 1997-EP873	19970224
	W: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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	AU 9720924	A	19970916	AU 1997-20924	19970224
	AU 706591	B2	19990617		
	EP 904110	A1	19990331	EP 1997-906115	19970224
	EP 904110	B1	20020724		
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	HU 9900993	A2	19990928	HU 1999-993	19970224
	JP 2000506133	T	20000523	JP 1997-530576	19970224
	EP 1221326	A2	20020710	EP 2002-8079	19970224
	EP 1221326	A3	20040114		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, SI, LT, FI				
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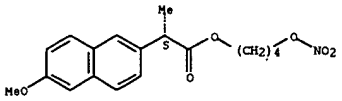
	RU 2192247	C2	20021110	RU 1998-117618	19970224
	PT 904110	T	20021231	PT 1997-906115	19970224
	ES 2180938	T3	20030216	ES 1997-906115	19970224
	US 2004242651	A1	20041202	US 2004-885121	20040707
	US 7087588	B2	20060808		
PRAI	IT 1996-MI352	A	19960226		
	EP 1997-906115	A3	19970224		
	WO 1997-EP873	W	19970224		
	US 1998-125878	B1	19980826		

AB Organic compds. containing the -ONO2 function, or inorg. compds. containing the -NO group, or compns. comprising these compds., are used to reduce the toxicity caused by drugs to the gastrointestinal, respiratory, and/or renal apparatus, the compds. being characterized in that they are nitric oxide (NO) donors, i.e. when they are put into contact in vitro with cells of the vasal endothelium or platelets.
IT 163133-43-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

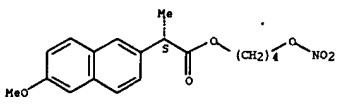
L14 ANSWER 41 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
(nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



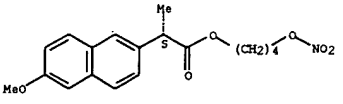
L14 ANSWER 42 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1997:180246 CAPLUS
DN 126:220449
TI NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects
AU Davies, N. M.; Roseth, A. G.; Appleyard, C. B.; Mcknight, W.; Del Soldato, P.; Calignano, A.; Cirino, G.; Wallace, J. L.
CS Intestinal Disease Research Unit, Faculty of Medicine, University of Calgary, Calgary, AB, Can.
SO Alimentary Pharmacology and Therapeutics (1997), 11(1), 69-79
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell
DT Journal
LA English
AB Studies were performed to determine if naproxen nitroxybutyl ester [NO-releasing naproxen (NO-naproxen)] was less ulcerogenic to the gastrointestinal tract than the parent naproxen, and if it exerted comparable analgesic and anti-inflammatory activities. The 2 drugs were compared in an acute gastric injury model, an antral ulcer model and after twice-daily administration for 18 days (small intestinal damage model) in rats. Anti-inflammatory activity was examined in the carrageenan-induced paw edema model in rats, while analgesia was examined in the HOAc-induced writhing model in mice. The pharmacokinetic profiles of naproxen vs. NO-naproxen were compared by HPLC. NO-naproxen produced less gastric damage than naproxen, despite inducing similar increases in plasma tumor necrosis factor-α. With chronic administration, small intestinal damage was markedly less with NO-naproxen than with the parent drug. However, NO-naproxen exerted analgesic effects superior to those of naproxen, and comparable anti-inflammatory effects. NO-naproxen was not completely converted to naproxen, but the lower plasma level of naproxen formed from NO-naproxen was not the underlying reason for the lower gastrointestinal toxicity of NO-naproxen. NO-naproxen represents a novel, gastrointestinal-sparing nonsteroidal anti-inflammatory drug with superior analgesic effects and comparable anti-inflammatory properties to those of naproxen.
IT 163133-43-5
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ulcerogenic, analgesic and anti-inflammatory effects of)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 43 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1996:333513 CAPLUS
DN 125:25397
TI Nitric oxide-releasing NSAIDs, a novel class of safe and effective anti-inflammatory agents
AU Del Soldato, P.; Cuzzolin, L.; Adami, A.; Conforti, A.; Crivellente, F.; Benoni, G.
CS Policlinico Borgo Roma, University of Verona, Verona, 37134, Italy
SO Inflammopharmacology (1996), 4(2), 181-188
CODEN: IAOAES; ISSN: 0925-4692
PB Kluwer
DT Journal; General Review
LA English
AB A review with 19 refs. The pharmacotoxicol. profile were reported for three new nitro-anti-inflammatory agents, nitrofenac, nitronaproxen and nitroflurbiprofen with the following results: in models of acute (carrageenan edema) and chronic (adjuvant arthritis) inflammation in the rat, the nitro derivs., compared with the parent drugs, showed similar anti-inflammatory properties by significantly inhibiting both edema volume and arthritis development. The nitroso compds. showed markedly less ulcerogenic activity compared with the parent drugs both in acute conditions and at the end of the chronic inflammation test. The lack of gastrointestinal damage observed with these new anti-inflammatory drugs is the consequence of their ability to release NO. This hypothesis is supported by pharmacokinetic studies and a significant increase in nitrite/nitrate plasma levels.
IT 163133-43-5, Nitronaproxen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-releasing nonsteroidal antiinflammatory agents)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

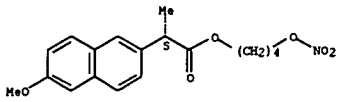
Absolute stereochemistry.



L14 ANSWER 44 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1996:253443 CAPLUS
DN 124:332273
TI Inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivatives with gastrointestinal-sparing properties
AU Cirino, G.; Wheeler-Jones, C. P. D.; Wallace, J. L.; Del Soldato, P.; Baydoun, A. R.
CS Vascular Biology Research Centre, King's College, London, W8 7AH, UK
SO British Journal of Pharmacology (1996), 117(7), 1421-6
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB The effects of novel nitric oxide-releasing nonsteroidal anti-inflammatory compds. (NO-NSAIDs) on induction of nitric oxide (NO) synthase by bacterial lipopolysaccharide (LPS) were examined in a murine cultured macrophage cell line, J774. LPS-induced nitrite production was markedly attenuated by the nitroxybutyl ester derivs. of flurbiprofen (FNBE), aspirin, ketoprofen, diclofenac and ketorolac, with each compound reducing accumulated nitrite levels by >40% at the maximum concns. (100 μg ml-1) used. Further examination revealed that nitrite production was inhibited in a concentration-dependent (1-100 μg ml-1) manner by FNBE which at 100 μg ml-1 decreased LPS stimulated levels by 63.3±8.6% (n=7). The parent compound flurbiprofen was relatively ineffective over the same concentration-range, inhibiting nitrite accumulation by 24±0.9% (n=3) at the maximum concentration used (100 μg ml-1). FNBE reduced LPS-induced nitrite production when added to cells up to 4 h after LPS. Thereafter, FNBE caused very little or no reduction in nitrite levels. Furthermore NO-NSAIDs (100 μg ml-1) did not inhibit the metabolism of L-[3H]-arginine to citrulline by NO synthase isolated from LPS-activated macrophages. Western blot anal. demonstrated that NO synthase expression was markedly attenuated following co-incubation of J774 cell with LPS (1 μg ml-1; 24 h) and FNBE (100μg ml-1; 24 h). Thus taken together, these findings indicate that NO-NSAIDs inhibit induction of NO synthase without directly affecting enzyme activity. In conclusion our results indicate that NO-NSAIDs can inhibit the inducible L-arginine-NO pathway, and are capable of suppressing NO synthesis by inhibiting expression of NO synthase. The clin. implications of these findings remain to be established.
IT 163133-43-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L14 ANSWER 44 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

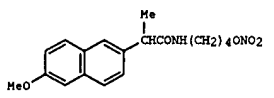


L14 ANSWER 45 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1995:667266 CAPLUS
DN 123:82961
TI Preparation of organic nitrate esters having antiinflammatory and/or analgesic activity
IN Del Soldato, Piero
PA Nicox Ltd., Ire.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9509831	A1	19950413	WO 1994-EP3182	19940923
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	GB 2283238	A	19950503	GB 1993-20599	19931006
	GB 2283238	B	19971126		
	CA 2173582	A1	19950413	CA 1994-2173582	19940923
	CA 2173582	C	20061128		
	AU 9478092	A	19950501	AU 1994-78092	19940923
	AU 678063	B2	19970515		
	EP 722434	A1	19960724	EP 1994-928801	19940923
	EP 722434	B1	19980729		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
	HU 74446	A2	19961230	HU 1996-874	19940923
	HU 218923	B	20001228		
	BR 9407749	A	19970212	BR 1994-7749	19940923
	JP 09503214	T	19970331	JP 1994-510585	19940923
	AT 168986	T	19980815	AT 1994-928801	19940923
	ES 2120070	T3	19981016	ES 1994-928801	19940923
	RU 2136653	C1	19990910	RU 1996-108907	19940923
	JP 3775796	B2	20060517	JP 1995-510585	19940923
	US 5700947	A	19971223	US 1996-624508	19960405
	US 5780495	A	19980714	US 1997-902570	19970729
PRAI	GB 1993-20599	A	19931006		
	IT 1994-MI916	A	19940510		
	WO 1994-EP3182	W	19940923		
	US 1996-624508	A3	19960405		

OS CASREACT 123:82961; MARPAT 123:82961
GI

L14 ANSWER 45 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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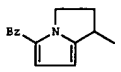
Q1=



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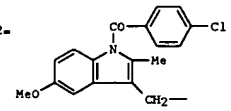
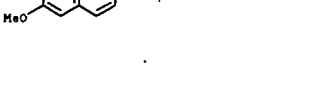
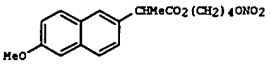


AB The title compds. MCOY[C(A)(B)]nONO2 [A, B = H, (un)branched alkyl; M = Q1, Q2, 2-(6-methoxy)naphthyl, etc.; n = 1-10], useful as analgesics, antiinflammatory agents, and blood platelet aggregation inhibitors, are prepared Thus, 2-(6-methoxy-2-naphthyl)propionic acid was converted into its Na carboxylate salt with NaOEt, the salt condensed with 1-bromo-4-chlorobutane, and the 4-chlorobutyl 2-(6-methoxy-2-naphthyl)propionate intermediate nitrated by reaction with AgNO3, producing the 4-nitratobutyl ester, II.
IT 170591-17-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of organic nitrate esters having antiinflammatory and/or analgesic activity)
RN 170591-17-0 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L14 ANSWER 46 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1995:498682 CAPLUS
DN 122:281711
TI Anti-inflammatory potency and gastrointestinal toxicity of a new compound, nitronaproxen
AU Cuzzolin, L.; Conforti, A.; Adami, A.; Lussignoli, S.; Menestrina, F.; Del Soldato, P.; Benoni, G.
CS Institute of Pharmacology, University of Verona, Verona, 37134, Italy
SO Pharmacological Research (1995), 31(1), 61-5
CODEN: PHMREP; ISSN: 1043-6618
DT Journal
LA English
GI

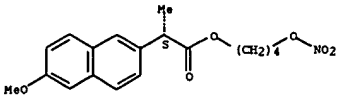


I

AB Naproxen and its derivative nitronaproxen (I) at the doses of 5 and 10 mg kg-1 were compared for their acute anti-inflammatory efficacy in a carrageenan edema model and gastrointestinal toxicity in rats. Moreover, the effects of the two drugs were evaluated in the adjuvant arthritis, after chronic doses of 4 and 8 mg kg-1 administered orally for 18 days. The edema reduction was maintained much longer (until 5 h) with nitronaproxen; the inhibition of arthritis was 50% or more with both doses of the examined drugs. From the histol. examination of the stomachs, an extensive mucosal vasocongestion and hemorrhagic lesions have been observed in some rats treated with naproxen. The percentages of animals with ulcers were 50, 100 and 10 with naproxen 6 and 18 mg kg-1 and nitronaproxen 54 mg kg-1, resp. A better gastrointestinal tolerability has been observed in arthritic and edemic rats treated with nitronaproxen compared to naproxen: this could be due to the presence of nitric oxide that acts in maintaining the tissue perfusion and integrity.
IT 163133-43-5, Nitronaproxen
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory activity and gastrointestinal toxicity of naproxen and nitronaproxen)
RN 163133-43-5 CAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L14 ANSWER 46 OF 46 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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L17            38 SEA FILE=CAPLUS ABB=ON  PLU=ON  "BENEDINI FRANCESCA"/AU
L18            76 SEA FILE=CAPLUS ABB=ON  PLU=ON  L15 OR L16 OR L17
L19             9 SEA FILE=CAPLUS ABB=ON  PLU=ON  L18 AND NAPROXEN

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L19 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:300267 CAPLUS
DN 142:349032
TI Nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity
IN Bolla, Manlio; Santus, Giancarlo; De Soldato, Piero
PA Nicox S.A., Fr.
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005030224	A1	20050407	WO 2004-EP51551	20040720
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI	EP 2003-292378	A	-20030926		

OS MARPAT 142:349032
AB The invention discloses the use of nitrosylated analgesic and/or antiinflammatory drugs for the prevention and/or treatment of viral diseases and/or their complications.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:203791 CAPLUS
DN 140:253349
TI Process for preparing nitrooxyalkyl esters of naproxen and bromonaproxen.
IN Del Soldato, Piero; Santus, Giancarlo; Benedini, Francesca
PA Nicox S.A., Fr.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004020384	A1	20040311	WO 2003-EP8698	20030806
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2497187	A1	20040311	CA 2003-2497187	20030806
	AU 2003266966	A1	20040319	AU 2003-266966	20030806
	EP 1532098	A1	20050525	EP 2003-747879	20030806
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	CN 1678560	A	20051005	CN 2003-820605	20030806
	JP 2005536558	T	20051202	JP 2004-532054	20030806
	NZ 537993	A	20061130	NZ 2003-537993	20030806
	ZA 2005000890	A	20060222	ZA 2005-890	20050131
	US 2006173005	A1	20060803	US 2005-523722	20050914
PRAI	IT 2002-MI1861	A	20020829		
	WO 2003-EP8698	W	20030806		

OS CASREACT 140:253349; MARPAT 140:253349
AB RCO2(CR1R2)m(CR3R4)n(CR5R6)oXp(CR7R8)q(CR9R10)r(CR11R12)sONO2 [R = naproxen, bromonaproxen residue; R1-R12 = H, alkyl, aralkyl; m, n, o, q, r, s = 0-6; p = 0, 1; X = O, S, SO, SO2, NR13, PR13, (substituted) cycloalkylene, arylene, heterocyclylene; R13 = H, alkyl], were prepared by reaction of RCO2Z (R as defined above; Z = H, Li+, Na+, K+, Ca++, Mg++, tetralkylammonium, tetralkylphosphonium) with Y(CR1R2)m(CR3R4)n(CR5R6)oXp(CR7R8)q(CR9R10)r(CR11R12)sONO2 [Y = halo, BF4, SbF6, FSO3, ASO3; A = (substituted) alkyl; other variables as defined above]. Thus, a mixture of naproxen and KHCO3 was heated in DMF at 50-60° for 90 min.; the mixture was cooled to room temperature and treated with KI and 4-bromobutyl nitrate (preparation given) followed by stirring for 25 h to give 73% naproxen 4-nitrooxybutyl ester.
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:115100 CAPLUS
DN 134:178355
TI Process for the preparation of naproxene nitroxyalkyl esters
IN Benedini, Francesca; Oldani, Erminio; Castaldi, Graziano; Tarquini, Antonio
PA Nicox S.A., Fr.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001010814	A1	20010215	WO 2000-EP7222	20000727
	W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2380116	A1	20010215	CA 2000-2380116	20000727
	EP 1200386	A1	20020502	EP 2000-951456	20000727
	EP 1200386	B1	20031001		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	TR 200200290	T2	20020521	TR 2002-290	20000727
	BR 2000012915	A	20020604	BR 2000-12915	20000727
	HU 200202435	A2	20021128	HU 2002-2435	20000727
	JP 2003506425	T	20030218	JP 2001-515282	20000727
	AT 251109	T	20031015	AT 2000-951456	20000727
	EP 1384707	A1	20040128	EP 2003-102132	20000727
	EP 1384707	B1	20050608		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, FI, CY				
	PT 1200386	T	20040227	PT 2000-951456	20000727
	ES 2208390	T3	20040616	ES 2000-951456	20000727
	AU 778694	B2	20041216	AU 2000-64385	20000727
	RU 2248348	C2	20050320	RU 2002-102860	20000727
	AT 297372	T	20050615	AT 2003-102132	20000727
	ES 2243859	T3	20051201	ES 2003-3102132	20000727
	ZA 2002000478	A	20030818	ZA 2002-478	20020118
	US 6700011	B1	20040302	US 2002-31412	20020118
	NO 2002000515	A	20020201	NO 2002-515	20020201
	ZA 2003004525	A	20040211	ZA 2003-4525	20030610
	US 2005119339	A1	20050602	US 2003-625558	20030724
PRAI	IT 1999-MI1753	A	19990804		
	EP 2000-951456	A3	20000727		
	WO 2000-EP7222	W	20000727		
	US 2002-31412	A3	20020118		

OS CASREACT 134:178355; MARPAT 134:178355
AB A process for obtaining nitroxyalkyl esters of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, was characterized in that a halide of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO2, wherein Y is a C2-C20 alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as defined containing a cycloalkylene as defined, in the presence of an inorg. base. E.g., to a solution of 4-nitroxybutan-1-ol and K2CO3 in

L19 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
dichloromethane is added 2-(S)-(6-methoxy-2-naphthyl)propanoic acid chloride. to give the 4-nitroxybutyl ester of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (85%, ee 98%).
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1999:257300 CAPLUS
DN 131:97177
TI Nitric oxide-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα
AU Fiorucci, S.; Santucci, L.; Federici, B.; Antonelli, E.; Distrutti, E.; Morelli, O.; Renzo, G. Di; Coata, G.; Cirino, G.; Soldato, P. Del ; Morelli, A.
CS Clinica di Gastroenterologia ed Epatologia, Policlinico Monteluce, Perugia, 06100, Italy
SO Alimentary Pharmacology and Therapeutics (1999), 13(3), 421-435
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB Background: Nitric oxide (NO)-releasing NSAIDs are a new class of NSAID derivs. with markedly reduced gastrointestinal toxicity. Although it has been demonstrated that NO-NSAIDs spare gastric mucosal blood flow, mol. determinants involved in this effect are unknown. Aim: To investigate the effect of aspirin, naproxen and flurbiprofen, and their NO-derivs., on gastric apoptosis and endothelial cell damage induced by tumor necrosis factor-α (TNFα). In other systems, TNFα-induced apoptosis is mediated by caspases, a growing family of cysteine proteases similar to the IL-1β converting enzyme (ICE), and so we have investigated whether NO-NSAIDs modulate ICE-like endopeptidases. Methods: Rats were treated orally with aspirin, naproxen and flurbiprofen, or their NO-releasing derivs. in equimolar doses, and were killed 3 h later to assess mucosal damage and caspase activity. Endothelial cells (HUVECs) were obtained from human umbilical cord by enzymic digestion. Caspase 1 and 3 activities were measured by a fluorimetric assay using selective peptides as substrates and inhibitors. Apoptosis was quantified by ELISA specific for histone-associated DNA fragments and by the terminal transferase nick-end translation method (TUNEL). Results: In vivo NSAID administration caused a time-dependent increase in gastric mucosal damage and caspase activity. NCX-4016, NO-naproxen and NO-flurbiprofen did not cause any mucosal damage and prevented cysteine protease activation. NSAIDs and NO-NSAIDs stimulated TNFα release. Exposure to TNFα resulted in a time- and concentration-dependent HUVEC apoptosis, an effect that was prevented by pretreating the cells with NCX-4016, NO-naproxen, NO-flurbiprofen, SNP or Z-VAD.FMK, a pan-caspase inhibitor. The activation of ICE-like cysteine proteases was required to mediate TNFα-induced apoptosis of HUVECs. Exogenous NO donors inhibited TNFα-induced cysteine protease activation. Inhibition of caspase activity was due to S-nitrosylation of ICE/CPP32-like proteases. NO-NSAIDs prevented IL-1β release from endotoxin-stimulated macrophages. Conclusions: NO-releasing NSAIDs are a new class of non-peptide caspase inhibitors. Inhibition of ICE-like cysteine proteases prevents endothelial cell damage induced by pro-inflammatory agents and might contribute to the gastro-protective effects of NO-NSAIDs.
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1997:433704 CAPLUS
DN 127:55916
TI Prompt-release pharmaceutical compositions
IN Santus, Giancarlo; Golzi, Roberto
PA Recordati S.A. Chemical and Pharmaceutical Company, Italy
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9718798	A1	19970529	WO 1996-EP5127	19961121
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9676948	A	19970611	AU 1996-76948	19961121
	EP 862421	A1	19980909	EP 1996-939871	19961121
	EP 862421	B1	20020731		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2000500477	T	20000118	JP 1997-519396	19961121
	AT 221372	T	20020815	AT 1996-939871	19961121
	US 6214386	B1	20010410	US 1996-754855	19961122
PRAI	IT 1995-MI2427	A	19951122		
	US 1995-8936P	P	19951220		
	WO 1996-EP5127	W	19961121		

AB A prompt-release pharmaceutical composition, suitable in particular for oral use, comprises (a) a plurality of nuclei having dimensions between 50 and 500 μm, selected among microcrystals of the active ingredient and microgranules containing at least one active ingredient and at least one pharmaceutically acceptable excipient, (b) a lipidic coating comprising a lipidic material sprayed in the melted state onto the nuclei, and optionally at least one hydrophilic additive, and (c) a vehicle comprising one or more pharmaceutically acceptable excipients. The coated micronuclei can form a suspension which can be reconstituted by the patient immediately before use by simply adding the suspending phase, or formed into tablets or solid aggregates. The active ingredient is selected among those having unpleasant palatability or taste, poor stability in the administration vehicle, and hygroscopicity. Microgranules were prepared from a mixture containing micronized diltiazem·HCl 600, micronized lactose 2100, and PVP 300 g and coated with melted lipid components containing glyceryl monostearate 90, white wax 8, cetyl alc. 1, and stearyl alc. 1 %. A dissoln. test according to USP showed a fast release of diltiazem.

L19 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1996:425623 CAPLUS
DN 125:96132
TI Liquid-suspension controlled-release pharmaceutical compositions of naproxen
IN Santus, Giancarlo; Bottoni, Giuseppe; Bilato, Ettore
PA Recordati S.A. Chemical and Pharmaceutical Company, Switz.
SO U.S., 10 pp., Cont.-in-part of U.S. 5,296,236.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5527545	A	19960618	US 1993-165307	19931210
	US 5296236	A	19940322	US 1992-928616	19920810
	US 5405619	A	19950411	US 1994-191013	19940201
	US 5510119	A	19960423	US 1995-394660	19950222
	US 5670171	A	19970923	US 1995-482092	19950607
PRAI	US 1989-408755	B1	19890918		
	US 1991-711588	B1	19910606		
	US 1992-928616	A2	19920810		
	IT 1992-MI2826	A	19921211		
	IT 1988-21961	A	19880916		
	US 1993-165307	A3	19931210		
	US 1994-191013	A1	19940201		

AB Disclosed is a liquid-suspension controlled-release enteric-coated pharmaceutical formulation for the administration of naproxen, comprising (a) microgranules of naproxen and an excipient; (b) four successive coats of polymeric hydrophilic and hydrophobic materials, at least the innermost of the coats imparting controlled-release properties to the naproxen according to a predetd. release profile, and at least the outermost of the coats imparting resistance to dissoln. in gastric fluids; and (c) a liquid administration vehicle. This composition enables the oral administration of naproxen as a single daily dose and avoids detrimental effects of prolonged contact of naproxen with the gastric mucosa thus aiding oral intake and minimizing the drug's typical side effects. For example, microgranules were prepared from a mixture containing naproxen, PVP, and lactose and coated with a 1st coating composition containing Et cellulose, di-Et phthalate, PEG, ethanol, and chloroform, followed by a 2nd hydrophilic coating composition containing Eudragit E, acetone, and iso-Pr alc., a 3rd lipophilic coating composition containing glyceryl monostearate, white beeswax, cetyl alc., stearyl alc., chloroform, and methanol, and a 4th enteric coating composition containing cellulose acetate phthalate, di-Et phthalate, acetone, and isopropanol.

L19 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1995:193659 CAPLUS
DN 123:208593
TI Preformulation studies on naproxen sodium suppositories
AU Santus, Giancarlo; Giordano, Ferdinando; Gazzaniga, Andrea; Bruni, Giovanna; Paiotti, Silvia
CS Recordati S.p.A., Milan, Italy
SO European Journal of Pharmaceutics and Biopharmaceutics (1994), 40(4), 243-5
CODEN: EJPBEL; ISSN: 0340-8159
DT Journal
LA English
AB Compatibility studies on a suppository formulation containing naproxen sodium (I), calcium levulinate (II), and a fat base are reported. DSC was mainly used for preformulation studies on the components, mixts., and reaction products. I and II interacted, depending on exptl. conditions, deeply modifying the technol. properties of suppositories.

L19 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1994:517705 CAPLUS
DN 121:117705
TI Controlled-release pharmaceutical suspensions containing naproxen
IN Santus, Giancarlo; Bottoni, Giuseppe; Bilato, Ettore
PA Recordati S.A. Chemical and Pharmaceutical Co., Switz.
SO Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 601508	A2	19940615	EP 1993-119587	19931206
	EP 601508	A3	19951025		
	EP 601508	B1	19990331		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	AT 178209	T	19990415	AT 1993-119587	19931206
	ES 2132163	T3	19990816	ES 1993-119587	19931206
	JP 06279274	A	19941004	JP 1993-310680	19931210
PRAI	IT 1992-MI2826	A	19921211		

AB Disclosed is a controlled-release enteric-coated pharmaceutical liquid suspension for the administration of naproxen (I) comprising (a) microgranules of naproxen and an excipient; (b) four successive coatings of polymeric hydrophilic and hydrophobic materials, the first applied of said coatings imparting controlled release properties to said naproxen according to a predetd. release profile; and (c) a liquid administration vehicle. This composition enables the oral administration of naproxen as a single daily dose and the adjustment of the dosage to a patient's requirements, thus aiding oral intake and minimizing the drug's typical side effects. A controlled-release oral suspension was prepared containing controlled-release microgranules of I 25.00, citric acid 0.75, Na citrate 0.5, microcryst. cellulose 5.50, Na CMC 0.50, tragacanth gum 1.30, Me p-hydroxybenzoate 0.25, Pr p-hydroxybenzoate 0.06, sorbitan monolaurate 0.05, di-Me siloxane 0.20, citrus flavoring 0.05, glycyrrhizinated ammonium 0.02, NaCl 0.05, and sugar 65.77 mg. The Cmax, Tmax, and AUC of I was 27.12, 6.0, and 946.51, as compared to 76.82 μg/h/mL, 2.3 h, and 1168.58 μg/mL, resp., for the immediate-release I granules.

L19 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1993:87640 CAPLUS
DN 118:87640
TI Controlled-release pharmaceutical composition with bioadhesive properties
IN Santus, Giancarlo; Bottoni, Giuseppe; Sala, Giovanni
PA Recordati S.A. Chemical and Pharmaceutical Co., Switz.
SO Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 516141	A1	19921202	EP 1992-109080	19920529
	EP 516141	B1	19960814		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
	JP 07215843	A	19950815	JP 1992-130545	19920522
	AT 141159	T	19960815	AT 1992-109080	19920529
	ES 2091363	T3	19961101	ES 1992-109080	19920529
PRAI	IT 1991-MI1486	A	19910530		

AB The title composition comprises a plurality of small size units coated with a bioadhesive polymer layer to ensure a gradual release of the active ingredient. The composition makes it possible to keep the release controlling function sep. from the function providing bioadhesion and can be adapted to oral, ocular, rectal, vaginal, nasal, or periodontal administration. Furosemide 50 parts were mixed with hydrogenated castor oil 50 parts and granulated and the resulting granules were mixed with Carbopol-934 33, and hydroxypropyl Me cellulose 33 parts and the mixture was then tabletted. The tablets then crumbled and sieved to obtain bioadhesive controlled-release granules with diameter of 300-600μm. The dissoln. profile of the bioadhesive granules were studied.

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L2              STRUCTURE UPLOADED
                D
L3              STRUCTURE UPLOADED
                D
L4            8 SEA SSS SAM L1 OR L2
L5           56 SEA SSS FUL L1 OR L2
L6           11 SEA SSS SAM L3
L7          377 SEA SSS FUL L3

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L9         5837 SEA ABB=ON  PLU=ON  L7
L10          10 SEA ABB=ON  PLU=ON  L8 AND L9
                D QUE L10 STAT
                D 1-10 BIB ABS HITSTR

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                D
L12           1 SEA SSS SAM L11
L13           3 SEA SSS FUL L11

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L14          46 SEA ABB=ON  PLU=ON  L13
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                D 1-46 BIB ABS HITSTR
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L15           3 SEA ABB=ON  PLU=ON  ("SOLDATO P DEL"/AU OR "SOLDATO PIERO"/AU
                OR "SOLDATO PIERO DEL"/AU)
                E SANTUS GIANCARLO/AU
L16          37 SEA ABB=ON  PLU=ON  "SANTUS GIANCARLO"/AU
                E BENEDINI FRANCESCA/AU
L17          38 SEA ABB=ON  PLU=ON  "BENEDINI FRANCESCA"/AU
L18          76 SEA ABB=ON  PLU=ON  L15 OR L16 OR L17
L19           9 SEA ABB=ON  PLU=ON  L18 AND NAPROXEN
                D QUE L19 STAT
                D 1-9 BIB ABS


     FILE HOME

     FILE REGISTRY
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     DICTIONARY FILE UPDATES:    2 JAN 2007  HIGHEST RN 916646-22-5

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